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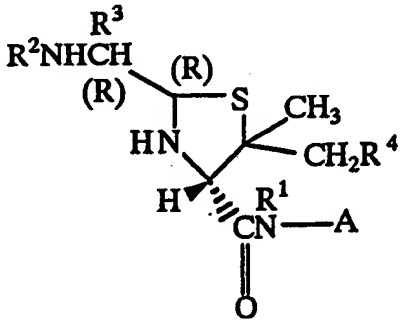
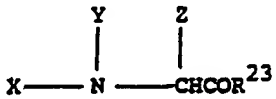


(I)



(II)

(57) Abstract

The present invention provides compounds of formula (I), wherein R^1 is hydrogen, alkyl or CH_2alkyl where the alkyl portion is substituted by OH; A represents either a group $CHR^{21}CHR^{22}OH$ or a group (II), where R^{21} is hydrogen, alkyl, cycloalkylalkyl or Aralkyl, R^{22} is hydrogen, alkyl, cycloalkylalkyl, aralkyl, $CHR^{24}CONR^{25}R^{26}$ (where R^{24} is hydrogen, alkyl, cycloalkylalkyl or Aralkyl, R^{25} is hydrogen or methyl and R^{26} is hydrogen, alkyl optionnally substituted by one or two hydroxyl groups, aryl, heteroaryl, cycloalkylalkyl, Aralkyl wherein the alkyl portion is optionnally substituted by hydroxymethyl, or Hetalkyl) or $CHR^{24}NHCOR^{27}$ (where R^{27} is alkyl, cycloalkylalkyl or an aralkyl), R^{23} is alkoxy or $NR^{28}R^{29}$ (where R^{28} is hydrogen or methyl and R^{29} is hydrogen, alkyl, aryl, aralkyl or cycloalkylalkyl); X is a group

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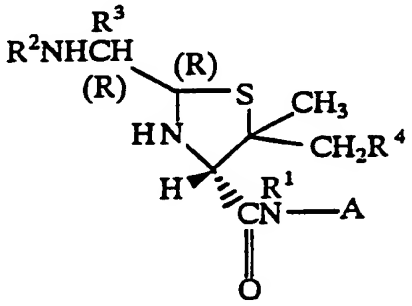
THIAZOLIDINE DERIVATIVES AND THEIR USE AS ANTI-VIRAL COMPOUNDS

The present invention relates to therapeutically active thiazolidine derivatives, processes for the manufacture of said compounds, pharmaceutical formulations containing said compounds and the use of said compounds in chemotherapy, more particularly in the therapy of viral infections.

Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Their presence has been associated with a wide range of diseases in humans and animals, and they are believed to be the causative agents in pathological states associated with many viruses including human immunodeficiency virus (HIV-1, HIV-2), the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host cells and is essential to the life cycle of the retrovirus. It has been demonstrated that retroviruses which lack the protease or contain a mutated form of it lack infectivity [cf. S. Crawford et al., J. Virol., 53, 899-907 (1985)]. Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

We have now found a novel group of compounds which are useful in the therapy of viral infections. More particularly, the compounds of the present invention inhibit proteases of retroviral origin and are therefore useful in the treatment of infections associated with retroviruses, especially AIDS and related conditions such as AIDS related complex (ARC) and lymphadenopathy.

Thus, in a first aspect, the present invention provides compounds of formula (I)



(I)

wherein :

R^1 is hydrogen, C_{1-4}alkyl or CH_2C_{1-3}alkyl where the C_{1-3}alkyl portion is substituted by OH;

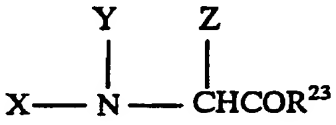
R^2 is hydrogen, C_{1-10}alkyl, C_{3-8}cycloalkyl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, COAr, COHet, $COCH_2R^5$, COCH(OH)Ar, COCH(OH)Het, COCH=CHPh, COR^6, CO_2CH_2Ar, CO_2CH_2Het, SO_2Ar, SO_2Het, $SO_2CH_2R^7$ SO_2CH=CHPh or SO_2R^8 [where R^5 and R^7 each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, aryloxy, heteroaryloxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_nCO_2R^9$ (where n is zero or 1 and R^9 is hydrogen or C_{1-6}alkyl), $(CH_2)_mNR^{10}R^{11}$ (where m is zero, 1, 2, 3, 4 or 5 and R^{10} and R^{11} are each independently hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), and R^6 and R^8 each independently represent C_{3-8}cycloalkyl substituted by phenyl];

R^3 is hydrogen, C_{1-6}alkyl, $COOR^{12}$ (where R^{12} is hydrogen, C_{1-6}alkyl or ArC_{1-4}alkyl) or $CONR^{13}R^{14}$ [where R^{13} is hydrogen or C_{1-4}alkyl and R^{14} is hydrogen, OH, aryl, heteroaryl, ArC_{1-4}alkyl, (wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl), $HetC_{1-4}$alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_pR^{15}$ (where p is zero or 1 and R^{15} is CF_3 or CO_2R^{16} where R^{16} is hydrogen or C_{1-6}alkyl), $(CH_2)qNR^{17}R^{18}$ (where q is zero, 1, 2, 3, 4 or 5 and R^{17} and R^{18} are each independently hydrogen, C_{1-4}alkyl or aryl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), $CHArCO_2R^{19}$, $CHHetCO_2R^{20}$ (where R^{19} and R^{20} are each independently hydrogen or C_{1-6}alkyl) or C_{1-6}alkyl optionally substituted

by OH, or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group];

R^4 is hydrogen, hydroxy, or acetoxy;

A represents either a group $CHR^{21}CHR^{22}OH$ or a group



[where R^{21} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl or ArC_{1-4}alkyl, R^{22} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl, ArC_{1-4}alkyl, $CHR^{24}CONR^{25}R^{26}$ (where R^{24} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl or ArC_{1-4}alkyl, R^{25} is hydrogen or methyl and R^{26} is hydrogen, C_{1-6}alkyl optionally substitued by one or two hydroxyl groups, aryl, heteroaryl, C_{3-8}cycloalkylC_{1-4}alkyl, ArC_{1-4}alkyl wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl, or HetC_{1-4}alkyl) or $CHR^{24}NHCOR^{27}$ (where R^{27} is C_{1-6} alkyl, C_{3-8} cycloalkylC_{1-4}alkyl or a ArC_{1-4}alkyl), R^{23} is C_{1-6}alkoxy or $NR^{28}R^{29}$ (where R^{28} is hydrogen or methyl and R^{29} is hydrogen, C_{1-6}alkyl, aryl, ArC_{1-4}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl);

X is a group

$$-CHR^{30}(CHR^{31})_r(CHR^{32})_sCHR^{33}-$$

where R^{30} and R^{33} are hydrogen, r is 1, s is zero and R^{31} is hydroxyl or hydroxymethyl, or R^{30} and R^{33} are hydrogen, r and s are 1 and R^{31} and R^{32} are each hydrogen or hydroxyl provided that at least one of R^{31} and R^{32} is hydroxyl, or one of R^{30} and R^{33} is hydrogen and the other is hydroxymethyl and r and s are zero;

Y is a methyl group and Z is a C_5 or C_6 cycloalkylmethyl group or Y and Z together represent a trimethylene or tetramethylene group in which one of the $-CH_2-$ groups is optionally replaced by -O-, -S- or $-NR^{34}-$ (where R^{34} is hydrogen, C_{1-6}alkyl, ArC_{1-4}alkyl, COR^{35}, CO_2R^{35} or $CONHR^{35}$ where R^{35} is C_{1-6}alkyl,

aryl, ArC_{1-4}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl) and one or more of the $-CH_2-$ groups is optionally substituted by a C_{1-6}alkyl, C_{1-6}alkoxy, aryl, ArC_{1-4}alkyl, ArC_{1-4}alkoxy or heteroaryl group or by two C_{1-6}alkyl groups, or Y and Z together represent a trimethylene or tetramethylene group fused to a benzene ring or to a 5 or 6 membered cycloalkane or cycloalkene ring];

and physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with organic or inorganic acids [for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates] and inorganic base salts such as alkali metal salts (for example sodium salts). The solvates may, for example, be hydrates.

Other salts which are not physiologically acceptable may be useful in the preparation of compounds of formula (I) and these form a further aspect of the invention.

In formula (I) hereinabove the ring carbon atom carrying the group R^2NHCHR^3- and the carbon atom carrying the groups R^2NH- and R^3 are in the R configuration. Where compounds of formula (I) contain one or more other chiral centres it is to be understood that the present invention encompasses the individual diastereoisomers of compounds of formula (I) as well as wholly or partially racemic mixtures thereof.

As used herein, the term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group. The term 'C_{3-8}cycloalkyl' as a group or part of a group includes, for example, cyclopropyl, cyclopentyl and cyclohexyl. The terms 'aryl' and 'Ar', as a group or part of a group respectively, mean a phenyl or naphthyl group optionally substituted by one or more suitable substituents. The terms 'heteroaryl' and 'Het', as a group or part of a group respectively, mean an optionally fused 5- or 6-membered heterocyclic group containing one or more heteroatoms selected from S, N and O and optionally substituted by one or more

suitable substituents. Suitable substituents referred to above within the definitions of 'aryl', 'Ar', 'heteroaryl' and 'Het' include halogen, C_{1-6}alkyl, a group $(CH_2)_rR^{36}$ [where r is zero, 1, 2, 3 or 4 and R^{36} is selected from OH, C_{1-3}alkoxy, CF_3, CN, NO_2, heteroaryl, CO_2R^{37} (where R^{37} is hydrogen or C_{1-6}alkyl), $CONR^{38}R^{39}$, $SO_2NR^{38}R^{39}$ or $NR^{38}R^{39}$ (where R^{38} and R^{39} each independently represent hydrogen, C_{1-4}alkyl or phenyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group)], phenyl, phenoxy and phenylC_{1-4}alkyl (such phenyl, phenoxy and phenylC_{1-4}alkyl substituents themselves optionally substituted in the phenyl ring by halogen, C_{1-3}alkyl, C_{1-3}alkoxy or CF_3). Examples of heterocyclic ring systems include thienyl, furyl, pyridyl, pyrrolyl, isothiazolyl, thiadiazolyl, oxazolyl, benzothienyl, benzofuryl, indolyl, quinolyl, thiazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, cinnolinyl, benzoxazolyl and benzimidazolyl. The term 'halogen' means fluorine, chlorine, bromine or iodine. The term 'saturated heterocyclic amino group' means a nitrogen linked cyclic amine group having 5, 6, 7 or 8 ring members and optionally containing in the ring -O- or -NR^{40}- (where R^{40} is hydrogen, C_{1-4}alkyl, aryl or ArC_{1-4}alkyl). The saturated heterocyclic amino group may for example have 5, 6 or 7 ring members and includes as examples pyrrolidino, piperidino, morpholino, piperazino, N-phenylpiperazino, homomorpholino and hexamethyleneimino.

Specific examples of the groups 'aryl' and 'Ar' include phenyl or phenyl substituted by F, Cl, di-Cl, OH, methyl, methoxy, CF_3, NO_2, CH_2OH, CO_2H, CO_2Bu-t, $(CH_2)_rNR^{38}R^{39}$ (where r is zero or 1 and R^{38} and R^{39} each independently represent hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a 5, 6 or 7 membered saturated heterocyclic amino group), phenyl or benzyl, and naphthyl or naphthyl substituted by ethoxy.

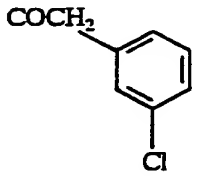
Specific examples of the groups 'heteroaryl' and 'Het' include 2, 3 or 4-pyridyl, 4-imidazolyl, 2 or 3-thienyl, 5-methyl-3-phenyl-4-isoxazolyl and benzimidazol-2-yl.

X specifically represents a group selected from $-CH(CH_2OH)CH_2-$, $-CH_2CH(CH_2OH)-$, $-CH_2CH(OH)CH_2-$, $-CH_2CH(CH_2OH)CH_2-$, $-CH_2CH(OH)CH_2CH_2-$, $-CH_2CH_2CH(OH)CH_2-$ and $-CH_2CH(OH)CH(OH)CH_2-$.

R^1 preferably represents a hydrogen atom or a methyl group.

R^2 preferably represents a group selected from COAr (where Ar is biphenyl), $COCH_2R^5$ (where R^5 is C_{1-6}alkyl, for example C_{1-4}alkyl such as isopropyl; aryl, for example phenyl optionally substituted by chlorine; heteroaryl, for example pyridyl; aryloxy, for example phenoxy; or ArC_{1-4}alkyl, for example $ArCH_2$ such as benzyl) or COR^6 (where R^6 is cyclopropyl substituted by phenyl).

Compounds in which R^2 represents $COCH_2Ph$,



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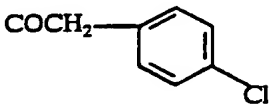

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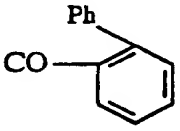

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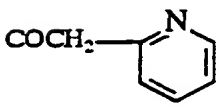

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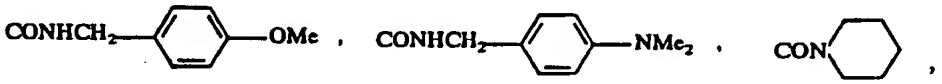
$COCH_2OPh$, $CO(CH_2)_2Ph$ or $COCH_2Pr\text{-}i$

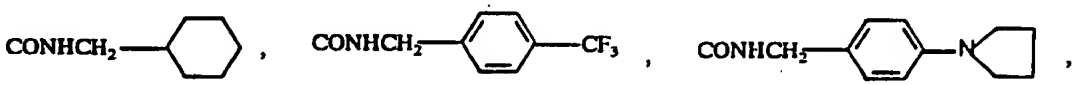
are particularly preferred.

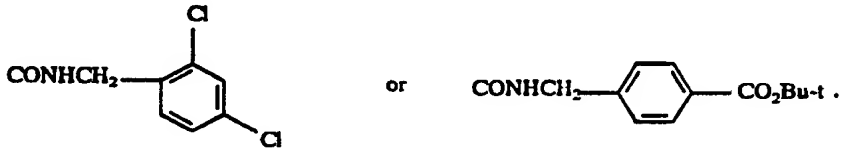
R^3 preferably represents a group $CONR^{13}R^{14}$ where R^{13} and R^{14} are as defined hereinabove. Such compounds in which R^{13} is hydrogen and R^{14} is a group selected from ArC_{1-4}alkyl (e.g. ArC_{1-2}alkyl where Ar is phenyl optionally substituted by CF_3, methoxy, $NR^{38}R^{39}$ where R^{38} and R^{39} each independently represent methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidino group, Cl, di-Cl or CO_2R^{37} where R^{37} is hydrogen or C_{1-4}alkyl e.g. t-butyl), $HetC_{1-4}$alkyl (e.g. $HetC_{1-2}$alkyl where Het is pyridyl, e.g. 2-pyridyl), C_{3-8}cycloalkylmethyl (e.g. cyclohexylmethyl) or CH_2CF_3 or R^{13} is hydrogen or methyl and R^{14} is methyl or ethyl or R^{13} and R^{14} together with the

nitrogen atom to which they are attached form a piperidino group are particularly preferred.

R^3 may particularly represent $CONHCH_2Ph$, $CONHCH_2CH_3$, $CONHCH_2CH_2Ph$, $CONMe_2$,







R^{22} preferably represents a group $CHR^{24}CONR^{25}R^{26}$ where R^{24}, R^{25} and R^{26} are as defined previously.

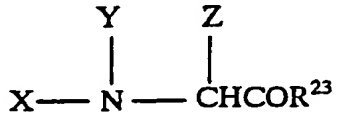
The group

$$\begin{matrix} R^1 \\ -NCHR^{21}CHR^{22}OH \end{matrix}$$

may particularly represent a group $-NHCHR^{21}CH(OH)CH_2CONHR^{26}$ where R^{21} and R^{26} are as defined previously. Compounds in which R^{21} represents ArC_{1-4}alkyl (e.g. benzyl) and R^{26} represents ArC_{1-4}alkyl (e.g. benzyl) or $HetC_{1-4}$alkyl (e.g. benzimidazol-2-ylmethyl) are preferred.

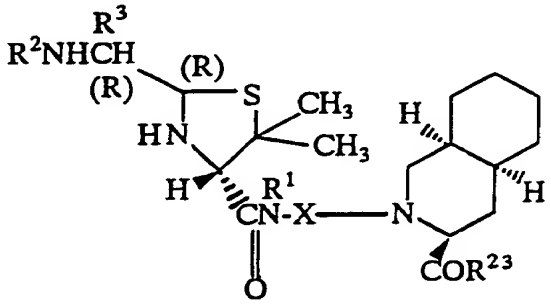
Examples of ring systems represented by NY-CHZ include thiazolidine, piperazine, piperidine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and decahydroisoquinoline.

A preferred group of compounds of the present invention are compounds of formula (I) in which A represents a group



where X and R^{23} are as defined above and the group NY-CHZ forms a monocyclic or bicyclic ring system as defined above.

A particularly preferred group of compounds of the invention are those of formula (Ia)



(Ia)

wherein R^1-R^3, R^{23} and X are as defined above, and physiologically acceptable salts and solvates thereof.

The group X as referred to in formulae (I) and (Ia) above may preferably represent $-CH_2CH(OH)CH_2-$.

The group R^{23} as referred to in formulae (I) and (Ia) above may preferably represent $NR^{28}R^{29}$, especially where R^{28} is hydrogen and R^{29} is C_{1-6}alkyl (e.g. t-butyl).

It is to be further understood that the present invention includes all combinations of the aforementioned preferred and particular groupings.

Particularly preferred compounds according to the invention are:

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-N-[[[(1,1-dimethylethoxy) carbonyl]amino]ethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-N-cylohexylmethyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-

isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-hydroxy-3-[[[(1,1-(dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-ethyl-4-[[[2-hydroxy-3-[[[(1,1-(dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-[4-[(dimethylamino)phenyl]methyl]-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,1''S,4a''S,8a''R]]]-5,5-dimethyl-4-[[[2-hydroxy-3-[1-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid methyl ester;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-α-[[4-(fluorophenyl)acetyl] amino]-4-[[[-3-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]-2-hydroxypropyl]amino]carbonyl]-N-(2-pyridinylmethyl)-2-thiazolidineacetamide;

and physiologically acceptable salts and solvates thereof.

Other preferred compounds according to the invention are 2R-[2α(R*),4β(2'S*,3''S*,4a''S*;8a''R*)]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-(2-phenyl-1-hydroxymethyl)ethyl]amino]carbonyl]-2-thiazolidineacetamide;

2R-[2α(R*),4β(R*,R*)-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[(2-hydroxy)-4-[[(1H-benzimidazol-2-yl)methyl]amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-thiazolidineacetamide; and

2R-[2α(R*),4β(R*,R*)-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[(2-hydroxy)-4-[(phenylmethyl)amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-thiazolidineacetamide

and physiologically acceptable salts and solvates thereof.

The compounds of the invention possess antiviral activity. In particular compounds of the invention are effective in inhibiting the replication of retroviruses, including human retroviruses such as human immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent, in particular as an antiviral agent, for example in the treatment of retroviral infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by a retrovirus such as HIV, in a mammal including man comprising administration of a therapeutically effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

There is also provided in a further or alternative aspect of the invention the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a viral infection, for example in the treatment of a retroviral infection.

The compounds of the invention are also potentially useful in the treatment of AIDS related conditions such as AIDS-related complex (ARC), progressive generalised lymphadenopathy (PGL), AIDS-related neurological conditions (such as dementia or tropical paraparesis), anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma and thrombocytopenia purpura.

The compounds of the invention are also useful in the prevention of progression to clinical illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of formula (I) or the physiologically acceptable salts or solvates thereof may also be used for the prevention of viral contamination of physiological fluids such as blood or semen in vitro.

Compounds of formula (I) may also be useful as intermediates in the preparation of other compounds of the invention.

The protease inhibiting properties of the compounds of the present invention can be demonstrated in vitro by their ability to inhibit the hydrolysis of an appropriate peptide substrate by HIV protease according to methods generally known in the art.

The antiviral activity of compounds of the invention may be demonstrated in vitro by their effect on cells infected with HIV-RF according to the following procedure :-

(a) C8166 cells were infected with HIV-1 (strain RF) at a moi of 1×10^{-3} infectious units/cell. Aliquots of 10^5 cells were added to each well of 24-well plates containing serial dilutions of test compounds at final concentrations of 50μg/ml to 0.05μg/ml in RPMI 1640 growth medium. Untreated infected cells and untreated uninfected cells were also included as controls. The plates were incubated at 37^0C/5% carbon dioxide for 3-4 days in humidified containers. The cells were examined daily for evidence of HIV-1 induced syncytium formation. The syncytia were quantified by reference to the untreated infected controls and the dose of compound required to reduce the cytopathic effect by 50% (EC_{50}) was calculated.

(b) Virus injections were prepared according to the inhibition of syncytium formation assay hereinabove. Supernatant fluids cleaved by centrifugation were assayed for p24 antigen using an ELISA kit. The synthesis of p24 core antigen was quantified by reference to the untreated infected controls and the dose of compound required to reduce the cytopathic effect by 50%. (EC_{50}) was calculated.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 1 to about 750mg/kg of bodyweight per day, such as about 3 to about 120mg per kilogram body weight of the recipient per

day, preferably in the range of 6 to 90mg/kg/day, most preferably in the range of 15 to 60mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500mg, conveniently 20 to 1000mg, most conveniently 50 to 700mg of active ingredient per unit dosage form.

Ideally the active ingredient should be adminsitered to achieve peak plasma concentrations of the active compound of from about 1 to about 75μM, preferably about 2 to 50μM, most preferably about 3 to about 30μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 100mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be

prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions

may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one more more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurised packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressurised pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose

or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with other therapeutic agents for example other antiinfective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof comprise a further aspect of the invention.

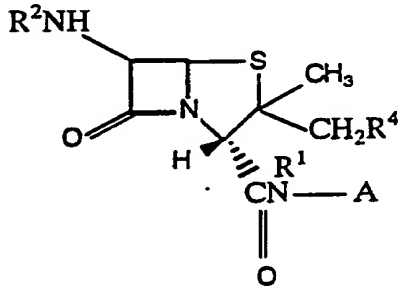
Suitable therapeutic agents for use in such combinations include (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (3TC), 3'-azido-3'-deoxythymidine (AZT), ribavirin, 3'-azido-2',3'-dideoxyuridine, acyclic nucleosides such as acyclovir, interferons such as α-interferon, renal excretion inhibitors such as probenicid, inhibitors of retroviral protease, 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine 2',3'-dideoxyinosine and 2',3'-dideoxy-2',3'- didehydrothymidine, non-nucleoside reverse transcriptase (RT) inhibitors including TIBO compounds (e.g. Janssen's R82150), HEPT compounds and Boehringer Ingleheim's RG587, immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoetin and ampligen.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Suitable methods for preparing compounds of formula (I) and their physiologically acceptable salts and solvates are described below.

Thus, in a first process (A), compounds of formula (I) in which R^3 represents $COOR^{12}$ or $CONR^{13}R^{14}$ may be prepared from compounds of formula (II)



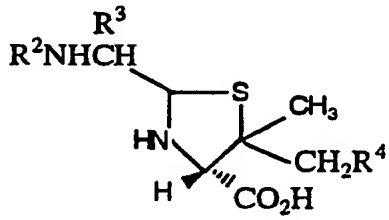
(II)

(wherein R^1, R^2, R^4 and A are as defined previously) or protected derivatives thereof by treating said compounds of formula (II) with an appropriate nucleophile $R^{12}OH$ or $R^{13}R^{14}NH$, followed, where necessary, by the removal of any protecting groups present.

The reaction is conveniently carried out in a suitable solvent such as water, a halogenated hydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran), an alcohol (e.g. ethanol or methanol) or a water-miscible solvent such as dimethylformamide or dimethylsulphoxide or a suitable mixture of such solvents at about room temperature, optionally in the presence of a suitable base such as an amine (eg diisopropylethylamine). When R^{13} and R^{14} both represent hydrogen atoms the amination reaction is conveniently effected using aqueous ammonia solution. When R^{12} is C_{1-6}alkyl or ArC_{1-4}alkyl the reaction is effected using an

alcohol $R^{12}OH$ or an alkali metal alkoxide (e.g. $NaOR^{12}$). When R^{12} is hydrogen the reaction is conveniently effected using a hydroxide such as sodium hydroxide.

In a further process (B) compounds of formula (I) may be prepared by coupling the carboxylic acids of formulae (III)



(III)

(wherein R^2-R^4 are as defined previously) or salts and/or protected derivatives thereof with an aminoalcohol of formula (IV)

$$HR^1NA \qquad (IV)$$

(wherein R^1 and A are as defined previously) or a protected derivative thereof, followed, where necessary, by the removal of any protecting groups present. The coupling may conveniently be effected in the presence of a coupling agent such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in the presence of a base such as N,N-diisopropylethylamine and in a suitable solvent (e.g. dimethylformamide) or N,N'-dicyclohexylcarbodiimide optionally in the presence of 1-hydroxybenzotriazole (or its hydrate) and in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or, more particularly, an ether (e.g. tetrahydrofuran). Under these conditions the reaction may conveniently be carried out at about room temperature. The coupling may alternatively be effected in the presence of ethyl chloroformate and N-ethylpiperidine in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane), conveniently at a temperature in the range of -20^0C to $+50^0C$.

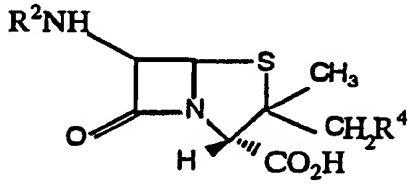
In another process (C) compounds of formula (I) may be converted to other compounds of formula (I).

In a particular embodiment of this process, compounds of formula (I) in which R^2 represents an acyl or sulphonyl group may be prepared from the

corresponding primary amine of formula (I) using conventional acylating or sulphonylating means. Thus, for example, a group CO_2CH_2Ar or CO_2CH_2Het may be introduced by reacting the amine with a haloformate (e.g. a chloroformate $ClCO_2CH_2Ar$ or $ClCO_2CH_2Het$) in a solvent such as water, preferably in the presence of a base such as an alkali metal carbonate (e.g. sodium carbonate). The amine may be regenerated from the so-formed grouping by treatment with an acid such as hydrobromic acid in acetic acid, conveniently in a solvent such as a halogenated hydrocabon (e.g. dichloromethane). A group COAr, COHet, $COCH_2R^5$, COCH=CHPh or COR^6 may be introduced by reacting the amine with an appropriate acid in the presence of an activator such as 1-(3-dimethylaminopropyl-3-ethylcardodiimide in a halogenated hydrocarbon solvent such as dichloromethane or in a solvent system comprising dioxane and water in the presence of triethylamine. Alternatively, the desired group may be introduced by reacting the amine with an anhydride in the presence of a suitable base such as an organic base (e.g. pyridine). A group SO_2Ar, SO_2Het, $SO_2CH_2R^7$, SO_2CH=CHPh or SO_2R^8 may be introduced by reacting the amine with an appropriate sulphonyl halide (e.g. a sulphonyl chloride) conveniently in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane) and preferable in the presence of a suitable base such as an organic base (e.g. triethylamine).

In another particular embodiment of process (C), compounds of formula (I) in which R^3 contains a carboxyl group may be prepared from the corresponding carboxylic acid ester of formula (I) using conventional means. Thus, for example, conversion of a t-butyl ester to be corresponding acid may conveniently be carried out by treating the ester with an acid such as hydrobromic acid in acetic acid, conveniently in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane).

Compounds of formula (II) may be prepared by coupling a carboxylic acid of formula (V)



(V)

(wherein R^2 and R^4 are as defined previously) or a salt thereof with an aminoalcohol of formula (IV) according to the procedure described in process (B) hereinabove.

Compounds of formula (III) in which R^3 represents $COOR^{12}$ or $CONR^{13}R^{14}$ may be prepared by treating the corresponding compounds of formula (V) with an appropriate nucleophile under the conditions described for process (A) hereinabove. Compounds of formula (III) in which R^3 represents C_{1-6}alkyl may be prepared from the corresponding compounds of formula (III) in which R^3 represents COOH using methodology well known to those of ordinary skill in the art.

Compounds of formulae (III) in which R^3 is hydrogen and compounds of formulae (IV) and (V) are either known compounds or may be prepared from the known compounds of formulae (III), (IV) and (V) using conventional means. Thus, for example, compounds of formula (IV) may be prepared according to the procedures illustrated in the Examples hereinafter.

It will be appreciated that some functional groups present in appropriate starting materials hereinabove may need to be protected, and deprotection may thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be carried out using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl or sulphonyl (e.g. allylsulphonyl or tosyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in 'Protective Groups in Organic Chemistry', Ed. J. F. W. McOmie (Plenum Press, 1973) or 'Protective Groups in Organic Synthesis' by

Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride. Carboxyl protecting groups may conveniently be protected using appropriate hydroxyl protecting groups above with deprotection effected according to the methods described above.

Particular isomers of formula (I) may either be prepared from starting materials having the desired stereochemistry or by epimerisation at an appropriate stage in the synthesis of the required compounds of formula (I). Epimerisation may be effected using conventional means, for example by treatment with an appropriate acid.

It will be appreciated that interconversions as outlined in process (C) above may also be carried out on appropriate intermediates such that the desired R^2 and R^3 groupings are introduced prior to the final step conversion reaction.

Compounds of formula (II) are novel intermediates and represent a further aspect of this invention.

When it is desired to prepare an acid addition salt of a compound of formula (I) the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) in the form of the free

base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol, ethanol or isopropanol).

Inorganic basic salts may be prepared by reacting the free base of a compound of formula (I) with a suitable base e.g. an alkoxide such as sodium methoxide optionally in the presence of a solvent (e.g. an alcohol such as methanol).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of formula (I) using conventional methods.

Solvates (e.g. hydrates) of a compound of formula (I) may be formed during the work-up procedure of one of the aforementioned process steps.

The following Preparations and Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^{0}C.

Intermediate 1

[3R,4S]-3-Hydroxy-4-[[(1,1-dimethylethyloxy)carbonyl]amino] benzenepentanoic acid

Described by P. Jouin et al., J. Chem. Soc., Perkin Transactions 1, 1987, 1177.

Intermediate 2

[2R-[2α,5α,6β]]-6-[[(4-Fluorophenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Described by G. L. Clark, W. I. Kaye, K. J. Pipenberg and N. C. Schieltz, Chemistry of Penicillin, H. T. Clark et al., Princeton University Press, 1949, 367-381.

Intermediate 3

[1'R,2'R]-N-[1-[2-Hydroxy-4-oxo-4[(phenylmethyl)amino]butyl]] carbamic acid,1.2-dimethylethyl ester

Diisopropylethylamine (220μl), benzylamine (124μl) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.4g) were added sequentially to a solution of Intermediate 1 (0.35g) in dimethylformamide (13ml). The solution was stirred at room temperature for 18h and then partitioned between ethyl acetate and water. The organic phase was washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform : methanol (25:1) as eluant to afford the title compound (0.42g) as a white solid, mp. 127-129°, $[\alpha]_D^{22}$ = + 27.3° (C=0.88 in methanol).

Intermediate 4

[1'R,2'R]-N-[1-[2-Hydroxy-4-oxo-1-phenylmethyl-4-[[(1H-benzimidazol-2-yl)methyl]amino]butyl]]carbamic acid,1,1-dimethylethyl ester

Diisopropylethylamine (660μl), 2-(aminomethyl)benzimidazole dihydrochloride hydrate (0.25g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.4g) were added sequentially to a solution of Intermediate 1 (0.35g) in dimethylformamide (13ml). The solution was stirred at room temperature for 18h and then partitioned between ethyl acetate and water. The precipitated solid was collected by filtration to give the title compound (0.24g) as a white solid, mp. 199-201°, $[\alpha]_D^{22}$ = + 26.4° (C=0.53 in dimethylsulphoxide).

Intermediate 5

[1'R,2'R]-N-[1-[2-Hydroxy-4-oxo-4-[(2-methylpropyl)amino]-1-(phenylmethyl)butyl]]carbamic acid,1,1-dimethylethyl ester

Diisopropylethylamine (450μl), isobutylamine (1.2ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.43g) were added sequentially to a solution of Intermediate 1 (0.37g) in dimethylformamide (15ml). The solution was stirred at room temperature for 16h and partitioned between ethyl acetate and water. The organic phase was washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and the

solvent evaporated in vacuo to leave a white solid. Purification by silica gel chromatography using chloroform/methanol (40:1) as eluant gave the title compound as a white solid (0.34g), mp. 139-141°, $[\alpha]_D$ = -43.9 (C=1.1 in methanol).

Intermediate 6

[2R-[2α,5α,6β]]-6-[[(4-Fluorophenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,N-ethylpiperidine salt

N-ethyl piperidine (3ml) in ether (55ml) was added to a solution of Intermediate 2 (7.7g) in ethyl acetate (ca. 200ml) to give a white precipitate. The mixture was stored at ca. 4° for 48h and then filtered to give the title compound (7.7g) as an off-white solid, mp. 133-135°, $[\alpha]_D^{22}$ = + 205° (C=1.0 in methanol).

Intermediate 7

[2R-[2α(R*),4β]]-5,5-Dimethyl-2-[2-oxo-1-[[(4-fluorophenyl)acetyl]amino]-2-[(2-pyridinylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid

2-Aminomethylpyridine (1.0ml) was added to a suspension of Intermediate 6 (1.5g) in dichloromethane (15ml) and the mixture stirred at 15h. Evaporation of the solvent in vacuo gave a yellow oil which was dissolved in ethyl acetate (30ml). Water (15ml) was added and the pH of the aqueous layer adjusted to pH 3.0 using 2M phosphoric acid. The organic layer was separated and the aqueous solution extracted with additional ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound as a white solid (0.81g), mp. 131-135°, $[\alpha]_D^{20}$ = + 61.2 (C=1.0 in methanol).

Intermediate 8

[2R-[2α(R*),4β]]-5,5-Dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(ethylamino)ethyl]-4-thiazolidinecarboxylic acid

Anhydrous ethylamine (12ml) in dichloromethane (50ml) at 0° was added to a solution of penicillin G N-ethyl piperidine salt (26.0g) in dichloromethane

(600ml). The mixture was stirred at 20° for 18h and the resulting suspension cooled to 0° for 20 min. The white solid was filtered off and washed with dichloromethane (100ml). The solid was suspended in a stirred mixture of water (200ml) and dichloromethane (200ml) and orthophosphoric acid was added to pH3.0. The organic phase was separated, washed with water (2 x 100ml) and brine (50ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound as a white solid (13.8g) m.p. 110-114° $[\alpha]_D^{22}$ = + 91.3° (c = 1.3 in methanol).

Intermediate 9

[2R-[2α(R*),4β]]-5,5-Dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[[[4-(dimethylamino)phenyl]methyl]amino]ethyl]-4-thiazolidinecarboxylic acid

Triethylamine (3.75ml) was added to a suspension of p-dimethylaminobenzylamine dihydrochloride (3.0g) in dichloromethane (60ml), followed by penicillin G N-ethyl piperidine salt (3.01g). The reaction mixture was stirred at room temperature for 18h and the solvent then evaporated in vacuo to give a solid. The solid was dissolved in a mixture of ethyl acetate (350ml) and water (150ml), and 2N phosphoric acid added to pH3.0. The aqueous layer was extracted with ethyl acetate (3 x 200ml) and the combined organic extracts washed with brine (200ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to afford a white solid. Purification by silica gel column chromatography using chloroform/methanol (40:1) as eluant gave the title compound (2.0g), m.p. 176-180°, $[\alpha]_D^{20}$ = + 95.5° (c = 1.05 in dimethylformamide).

Intermediate 10

[2R-[2α(R*),4β]]-5,5-Dimethyl-2-[2-oxo-1-[[1,1'-biphenyl]-4-ylcarbonyl]amino]-2-(ethylamino)ethyl]-4-thiazolidinecarboxylic acid

Anhydrous ethylamine (3ml) was added to a solution of [2R-[2α,5α,6β]]-6-[([1,1'-biphenyl]-6-ylcarbonyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid[1] (3.0g) in dichloromethane (80ml) at 0°. The mixture was stirred at room temperature for 17h and then partitioned

between ethyl acetate (150ml) and water (50ml). 2N Phosphoric acid was added to pH3.0 and the aqueous layer extracted with ethyl acetate (2x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to afford a white solid. Recrystallisation from methanol/diethyl ether gave the title compound (0.7g), m.p. 133-136°, $[\alpha]_D^{23}$ = +51.7° (c = 1.1 in methanol).

1. R Kinget and M Schwartz, J.Pharm.Sci, 1969, 58(9), 1103.

Intermediate 11

[3R,4S]-3-Hydroxy-4-[[(1,1-dimethylethoxy)carbonyl]amino] benzenepentanoic acid, ethyl ester

2.5M Butyl lithium (53ml) was added to a solution of diisopropylamine (18ml) in dry tetrahydrofuran (250ml) at -10° and after 15 min the temperature was lowered to -78°. Dry ethyl acetate (12.7ml) was added and the solution stirred for a further 15 min. Boc-(R)-phenylalaninal (23.8g; Y. Sasaki et al., J. Med. Chem., 1987, 30 1162) in tetrahydrofuran (150ml) was added dropwise and after stirring for 15 min 2N hydrochloric acid was added, the cooling bath removed and the pH adjusted to pH 2-3 with a further quantity of 2N hydrochloric acid. The mixture was extracted with ethyl acetate and the organic extract washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The ethyl acetate solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a solid. 3g of this product was purified by silica gel chromatography using ethyl acetate/cyclohexane (1:4) as eluant to afford after recrystallisation from ethyl acetate/cyclohexane the title compound (0.95g), mp. 86-88°, $[\alpha]_D^{21}$ = +34.1° (C=0.9 in methanol).

Intermediate 12

[1'R,2'R]-N-[1-[3-(Aminocarbonyl)-2-hydroxy-1-(phenylmethyl) propyl]]carbamic acid-1,1-dimethylethyl ester

Intermediate 11 was dissolved in methanol (5ml) at 0° and ammonia bubbled through the solution for 1h. The solution was stirred at room temperature for three days and excess ammonia removed by bubbling nitrogen. The solvent was evaporated in vacuo and the resulting solid purified by silica gel chromatography using chloroform/methanol (10:1) as eluant to afford the title compound (0.35g) as a white solid, mp. 173-175°, $[\alpha]_D^{23}$ = +44.4° (C=0.54 in methanol).

Intermediate 13

N-(2-Propenyl)carbamic acid, 1,1-dimethylethyl ester

2-Propenamine (1.0g) in chloroform (1ml) was added to a mixture of di-tert-butyldicarbonate (3.8g) in chloroform (10ml) over 5 min at 0°. After 1h a solution of 1M phosphoric acid (20ml) was added and the layers separated. The organic phase was washed with saturated sodium hydrogen carbonate solution (20ml) and brine (20ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to an oil, which crystallised on standing to give the title compound (2.8g), m.p. 35-37°.

Intermediate 14

[2'RS]-N-(2-Oxiranylmethyl)carbamic acid, 1,1-dimethylethyl ester

Intermediate 13 (2.7g) in dichloromethane (100ml) was stirred at room temperature with meta-chloroperbenzoic acid (6.0g) for 3h. A solution of sodium sulphite (8.0g in water 10% w/v) was then added and stirring continued for 30 min. The layers were then separated and the organic phase washed with saturated sodium hydrogen carbonate (50ml), dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound as a clear oil (2.5g), ^1H nmr ($CDCl_3$) δ 1.48 (9H), 2.60 (1H), 2.80 (1H), 3.10 (1H), 3.22 (1H), 3.55 (1H) and 4.75 (1H).

Intermediate 15

[2'RS, 3" S, 4a "R, 8a"S]-N-[2-Hydroxy-3-[3-[[(1,1-dimethylethyl)amino]carbonyl]-decahydro-2-isoquinolinyl]propyl]carbamic acid, 1,1-dimethylethyl ester

Intermediate 14 (0.1g) was added to a solution of [3S-[3α,4aα,8aα]]-decahydro-N-(1,1-dimethylethyl)-3-isoquinoline carboxamide[2] (0.14g) in ethanol (5ml) and the solution stirred for 72h at room temperature under nitrogen. The solvent was then evaporated in vacuo to give a clear oil, which was purified by silica gel column chromatography (Merck 9385, 20g) using chloroform/methanol (80:1) to give two diastereoisomers of the title compound:-

Isomer 1, 95mg, ^{1}H nmr (DMSO-d_6) δ 1.25(9H), 1.38(9H), 1.1 to 2.1(14H), 2.25(1H), 2.7 to 3.0(3H), 3.3 to 3.5 (1H), 3.58(1H), 4.75(1H), 6.68(1H) and 7.36(1H), mass spec. [MH^+] 412.5.

Isomer 2, 92mg, ^{1}H nmr (DMSO-d_6) δ 1.25(9H), 1.38(9H), 1.2 to 2.2(14H), 2.30(1H), 2.4 to 2.6(1H), 2.80(1H), 3.02(2H), 3.58(1H), 4.65(1H), 6.76(1H) and 7.36(1H), mass spec. [MH^+] 412.5.

2. K.E.B. Parkes, S. Redshaw and G.J. Thomas, EP-A-0432694.

Intermediate 16

(S)-2-[[(1,1-Dimethylethyl)amino]carbonyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester.

(S)-1,2-Piperidinedicarboxylic acid,1-(1,1-dimethylethyl ester) (510mg) was dissolved in dry dimethylformamide (10ml) and N-ethyldiisopropylamine (430μl),2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (127mg) and tert-butylamine (260μl) added. The solution was stirred for 72h under N_2 at room temperature. Water (30ml) was then added and the solution extracted with ethyl acetate (3 x 20ml). The combined organic fractions were then washed with saturated sodium hydrogen carbonate (20ml) and saturated sodium chloride solution (20ml), dried and concentrated to give the title compound (600mg) as on off-white solid, mp. 125-127°, ^{1}H n.m.r. (DMSO-d_6), δ 1.26 (9H), 1.36 (9H), 1.1-1.7 (5H), 1.94 (1H), 3.17 (1H), 3.74 (1H), 4.40 (1H), 7.26 (1H), mass spec. [MH^+] 285.4.

Intermediate 17

[2RS, 2'S]-N-[2-Hydroxy-3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-piperidinyl]propyl]carbamic acid, 1,1-dimethylethyl ester.

Intermediate 16 (580mg) in 1,4-dioxan (10ml) was stirred for 4h with 3.3M hydrogen chloride in 1,4-dioxan (6ml). The mixture was concentrated to an off-white solid and re-dissolved in ethanol (10ml) to which was added N-ethyldiisopropylamine (0.39ml) and Intermediate 14 (350mg). The solution was stirred for 20h at room temperature under nitrogen. The reaction mixture was then concentrated to an oil and purified by column chromatography on silica gel (Merck 9385, 150g) using chloroform : methanol (70:1) to give both stereoisomers of the title compound.

Isomer 1, eluted first, isolated as a white solid (172mg), ^{1}H n.m.r. (DMSO-d_6), δ 1.26 (9H)., 1.36 (9H), 1.2-1.8 (6H), 1.89 (1H), 2.02 (1H), 2.2 (1H), 2.86 (2H), 3.02 (1H), 3.64 (1H), 4.91 (1H), 6.70 (1H), 7.28 (1H).

Isomer 2, eluted second, isolated as a white solid (129mg), mp. 48-52, ^{1}H n.m.r. (DMSO-d_6), δ 1.21 (9H), 1.30 (9H), 1.2-1.7 (6H)), 1.88 (1H), 2.00 (1H), 2.28 (1H), 2.7-3.2 (3H), 3.58 (1H), 4.67 (1H), 6.69 (1H), 7.13 (1H).

Intermediate 18

[1'R,2'R,1''S]-N-[2-Hydroxy-4-[[2-hydroxy-1-(phenylmethyl) ethyl]amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid,1,1-dimethylethyl ester

Diisopropylethylamine (126μl), S-phenylalaninol (109mg) and 2-(1H-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (229mg) were added sequentially to a solution of Intermediate 1 (200mg) in dimethylformamide (8ml). The solution was stirred at room temperature for 18h and then partitioned between ethyl acetate and water. The organic phase was washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform:methanol (20:1) as eluant to afford the title compound (243mg) as a white solid, mp. 141-143°, $[\alpha]_D^{22}$ = +3.4° (c 0.58, methanol).

Intermediate 19

[1'R,2'R,1''R]-N-[2-Hydroxy-4-[[2-hydroxy-1-phenylmethyl)ethyl]amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid,1,1-dimethylethyl ester

Diisopropylethylamine (126μl), R-phenylalaninol (109mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (229mg) were added sequentially to a solution of Intermediate 1 (200mg) in dimethylformamide (8ml). The solution was stirred at room temperature for 18h and then partitioned between ethyl acetate and water. The organic phase was washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform:methanol (20:1) as eluant to afford the title compound (170mg) as a white solid, mp. 135-137°, $[\alpha]_D^{22}$ +41.3° (c 0.52, methanol).

Intermediate 20

[1'R,2'R,1''R]-N-[2-Hydroxy-4-[[2-hydroxy-1-(phenylethyl]amino]-4-oxo-1-phenylmethyl)butyl]carbamic acid 1,1-dimethylethyl ester

Diisopropylethylamine (126μl), S-phenylglycinol (99mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (229mg) were added sequentially to a solution of Intermediate 1 (200mg) in dimethylformamide (5ml). The solution was stirred at room temperature for 16h and then partitioned between ethyl acetate and water. The organic phase was washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The reside was purifed by silica gel chromatography using chloroform : methanol (20:1) as eluant to afford the title compound (220mg) as a white solid, mp. 162-163°, $[\alpha]_D^{23}$ +54.5° (c 0.55, methanol).

Intermediate 21

[1'R,2'R,1''S]-N-[2-Hydroxy-4-[[2-hydroxy-1-phenylethyl]amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid 1,1-dimethylethyl ester

Diisopropylethylamine (126μl), R-phenylglycinol (99mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (229mg) were added sequentially to a solution of Intermediate 1 (200mg) in dimethylformamide (5ml). The solution was stirred at room temperature for 18h and then partitioned between ethyl acetate and water. The organic phase was washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform : methanol (20:1) as eluant to afford the title compound (173mg) as a white solid, mp. 154-156°, $[\alpha]_D^{22}$ 0° (c 0.54, methanol).

Intermediate 22

[1'R,2'R]-N-[2-Hydroxy-4-[(2,3-dihydroxypropyl)amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid 1,1-dimethylethyl ester

Diisopropylethylamine (248μl), (RS)-3-amino-1-propanediol (118mg) and 2-(1N-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (457mg) were added sequentially to a solution of Intermediate 1 (400mg) in dimethylformamide (12ml). The solution was stirred at room temperature for 1½h and then partitioned between ethyl acetate and water. The organic phase was washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried (($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform : methanol (30:1 to 5:1) as eluant to afford the title compound (139mg) as a colourless oil, $[\alpha]_D^{23}$ +29.0° (c 0.26, methanol), ^1H n.m.r. (DMSO-d_6) δ 1.30 (9H), 2.19 (2H), 2.4-2.7 (1H), 2.7-2.9 (1H), 2.9-3.1 (2H), 3.1-3.3 (3H), 3.49 (1H), 3.62 (1H), 3.88 (1H), 4.70 (1H), 4.90 (1H), 6.46 (1H), 7.1-7.4 (5H) and 7.80 (1H).

Intermediate 23

[1'R,2'R,2''RS]-N-[2-Hydroxy-4-[(3-hydroxypropyl)amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid 1,1-dimethylethyl ester

Diisopropylethylamine (186μl), 3-amino-1-propanol (74μl) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (343mg) were added sequentially to a solution of Intermediate 1 (300mg) in dimethylformamide (10ml). The solution was stirred at room temperature for 1.5h and then partitioned between ethyl acetate and water. The organic phase was washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried (($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform : methanol (40:1 to 25:1) as eluant to afford the title compound (244mg) as a white solid, mp. 59-63° softens, $[\alpha]_D^{23}$ +34.1° (c 1.11, methanol).

Intermediate 24

[1'R,2'R]-N-[2-Hydroxy-4-[[2-(1H-imidazol-2-yl)ethyl]amino]-4-oxo-1-(phenylmethyl)butyl]carbamic acid 1,1-dimethylethyl ester

Diisopropylethylamine (218μl), histamine (126mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (400mg) were added to a solution of Intermediate 1 (350mg) in dimethylformamide (10ml). The solution was stirred at room temperature for 1.25h and then partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform : methanol (20:1 to 5:1) as eluant to afford the title compound (125mg) as a white solid, mp. 157-159°, $[\alpha]_D^{23}$ +27.5° (c 1.1, methanol).

Intermediate 25

(1'R)-N-[3-Chloro-2-oxo-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester

N-Benzyloxycarbonyl-D-phenylalanine (1.5g) in tetrahydrofuran (12.6ml) was stirred at -15° and triethylamine (0.73ml) and ethyl chloroformate (0.5ml) added. After stirring at this temperature for a further 20min, the white precipitate was filtered and the filtrate was added to an ethereal solution of diazomethane

[30ml; prepared from diazald (1.4g)] in a salt-ice bath. After stirring for 30min, the yellow solution was set aside to warm to room temperature overnight. Then a stream of hydrogen chloride gas was bubbled through the solution until the colour was discharged. The mixture was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate, dilute hydrochloric acid, saturated sodium hydrogen carbonate and saturated sodium chloride solution. The organic layer was dried and evaporated to a colourless mass which was recrystallized from 75% aqueous ethanol to afford the title compound (644mg) as a white solid, mp. 101-102°, $[\alpha]_D^{21}$-25.85° (c 0.56, $CHCl_3$).

Intermediate 26

[1'R,2''RS]-N-[3-Chloro-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester

A solution of Intermediate 25 (17.12g) in tetrahydrofuran (250ml) and water (100ml) was stirred in an ice-bath and sodium borohydride (2.87g) added. After stirring at this temperature for 1.5h, the solvent was evaporated to a solid residue, which was suspended in chloroform before adding water to give a clear solution. Following adjustment of pH to ca. 1 with addition of dilute hydrochloric acid, the organic layer was separated, dried and evaporated to a white solid which contained both R,R- and R,S-diastereomers. The crude product was recrystallized from a mixture of ethyl acetate and cyclohexane (4:1) to afford the less soluble major isomer as a white solid (7.24g), mp. 142-144°, $[\alpha]_D^{21}$ +32.16° (c 0.59, DMSO), ^1H n.m.r. ($CDCl_3$) δ 2.87-3.06 (3H), 3.50-3.71 (2H), 3.85 (1H), 3.99 (1H), 4.80 (1H), 5.03 (2H), 7.13-7.40 (10H). The mother liquor was concentrated to give the title compound (10.55g) as a gummy solid which contained ca. equal amounts of both diastereomers, i.r. ($CHBr_3$) γ 3600, 3425, 2105, 1712 and 1508cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 2.7-3.3 (3H), 3.4-4.3 (4H), 4.5-5.4 (3H) and 7.0-7.5 (10H).

Intermediate 27

[1'R,2''RS]-N-[3-Azido-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester

A mixture of Intermediate 26 (10.57g) and sodium azide (3.69g) in N,N-dimethylformamide (100ml) was heated at 90° for 18h. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with water, dried and evaporated to leave a brown gum which was purified by column chromatography on silica gel (Merck Kieselgel 60, 200g) using chloroform/methanol (95:5) as eluant to afford the title compound (7.57g) as a pale yellow solid, mp. 67-69°, $[\alpha]_D^{21.5}$ +41.36° (c 0.67, DMSO).

Intermediate 28

[1'R,2''RS]-N-[3-Amino-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester

A mixture of Intermediate 27 (7.50g) and triphenylphosphine (5.94g) was dissolved in 60% aqueous tetrahydrofuran (400ml) and then heated under reflux for 23h. After cooling the clear solution was diluted with ethyl acetate and extracted with 2M hydrochloric acid. The aqueous extracts were combined, treated with sodium hydrogen carbonate until basic and back-extracted into ethyl acetate. The organic layer was dried and evaporated to give the title compound (4.77g) as a foam, $[\alpha]_D^{21.5}$ +34.76° (c 0.67, DMSO), ^{1}H n.m.r. ($CDCl_3$) δ 2.6-3.2 (4H), 3.4-4.1 (5H), 4.8-5.15 (2H), 5.25-5.7 (1H) and 7.0-7.8 (10H).

Intermediate 29

[1'R,2'RS]-N-[2-Hydroxy-1-(phenylmethyl)-3-[[(phenylmethyl) carbonyl] amino]propyl]carbamic acid, phenylmethyl ester

Intermediate 28 (4.44g) in dichloromethane (340ml) was stirred with 1-hydroxybenzotriazole (2.29g), phenylacetic acid (2.36g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.26g) at room temperature for 17h. The mixture was partitioned between dichloromethane and water. The organic layer was separated, washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and evaporated to a white solid which was recrystallized from methanol to afford the

title compound (1.92g) as a white solid, mp. 182-186° (dec.), $[\alpha]_D^{23}$ +27.46° (c 0.51, DMSO).

Intermediate 30

[2'RS,3'R]-N-[3-Amino-2-hydroxy-4-(phenylbutyl)benzeneacetamide

Intermediate 29 (500mg) in ethanol (280ml) was hydrogenated with 10% palladium-on-charcoal (682mg) under normal pressure and at ambient temperature for 5h. After degassing, the mixture was filtered through Kieselguhr. The filtrate was evaporated to leave the title compound (302mg) as a gum, i.r. (DMSO-d_6) γ_{max} 3600-3000, 1664 and 1535cm^{-1}, ^{1}H n.m.r. (DMSO-d_6) δ 2.3-3.8 (10H), 4.3-5.1 (1H), 6.9-7.7 (10H) and 8.0 (1H).

Intermediate 31

(3S)-1,2,3,4-Tetrahydro-3-[[(1,1-dimethylethyl)amino]carbonyl]-2-isoquinolinecarboxylic acid, 1,1-dimethylethyl ester

(3S)-1,2,3,4-Tetrahydro-2,3-isoquinolinedicarboxylic acid,2-(1,1-dimethylethyl ester)[3] (3.26g) in a mixture of N,N-dimethylformamide (10ml) and dichloromethane (120ml) was stirred at room temperature with tert-butylamine (2.79ml), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.50g) and 1-hydroxybenzotriazole (3.46g) for 20.5h. The reaction mixture was diluted with dichloromethane and then washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and concentrated to a brown oil which was purified by column chromatography on silica gel (Merck Kieselgel 60, 200g) using dichloromethane/methanol (9:1) as eluant to afford the title compound (2.03g) as a gum, $[\alpha]_D^{20}$ -3.4° (c 0.67,$CHCl_3$), ^{1}H n.m.r. ($CDCl_3$) δ 1.12 (9H), 1.48 (9H), 2.5-3.8 (2H), 4.2-4.8 (3H) and 7.1-7.4 (5H).

3. V.J. Hruby et al., Collect. Czech. Chem. Commun., 1988, 53 (11A), 2549-73.

Intermediate 32

(3S)-N-(1,1-Dimethylethyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide hydrochloride

Intermediate 31 (2.01g) in 1,4-dioxan (20ml) was stirred for 19h with 8.5M hydrogen chloride in 1,4-dioxan (8.5ml). The mixture was concentrated to give the title compound (0.87g) as a white solid, mp. 252-254°, $[\alpha]_D^{20}$ -107.2° (c 0.57, DMSO).

Intermediate 33

[2'RS,3''S]-N-[3-[3-[[(1,1-Dimethylethyl)amino]carbonyl]-1,2,3,4-tetrahydro-2-isoquinolinyl]-2-hydroxypropyl] carbamic acid,1,1-dimethylethyl ester

Intermediate 32 (435mg) in ethanol (13.5ml) was stirred at room temperature with diisopropylethylamine (343μl) and Intermediate 14 (352mg) for 3 days and then at 65° for 7h. The reaction mixture was diluted with ethyl acetate and washed with 0.5M hydrochloric acid, saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and evaportated to leave a gum which was purified by column chromatography on silica gel (Merck Kieselgel 60, 30g) using dichloromethane/methanol (9:1) as eluant to give the title compound (657mg) as a colourless gum which contained both diastereomers, $[\alpha]_D^{20}$ -12.3° (c 0.49,DMSO), ^{1}H n.m.r. (DMSO-d_6) δ 1.2-1.6 (18H), 2.2-2.7 (3H), 2.8-3.5 (4H), 3.5-4.1 (3H), 4.8-5.3 (1H), 6.5-7.0 (1H), 7.0-7.3 (4H) and 7.5-7.7 (1H).

Intermediate 34

[3S,2''RS]-2-[3-Amino-2-hydroxypropyl]-N-(1,1-dimethylethyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide, hydrochloride

Intermediate 33 (644mg) in 1,4-dioxan (16ml) was stirred for 20h with 8.5M hydrogen chloride in 1,4-dioxan (2.1ml). The reaction mixture was concentrated to give the title compound (544mg) as a yellow foam, $[\alpha]_D^{19}$ -27.7° (c O.49, DMSO), ^{1}H n.m.r. (DMSO-d_6) δ 1.18 (9H), 2.5-4.7 (10H + exchangeable protons), 7.0-7.3 (4H) and 7.7-8.6 (1H).

Intermediate 35

[3S-[3S-[3α,4αβ,8αβ],2'RS,2''S,5''R,6''R]]-N-(1,1-Dimethylethyl)-2-[3-[[3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]hept-2-ylcarbonyl]amino]-2-hydroxypropyl]decahydro-3-isoquinolinecarboxamide

6M Hydrogen chloride in dioxan (3ml) was added to Intermediate 15 as a mixture of diastereoisomers (0.5g) in dioxan (5ml) at room temperature. The solution was stirred at room temperature for 2h and the solvent then removed in vacuo to afford a white solid (0.48g). The salt was disolved in dimethylformamide (20ml) and diisopropylethylamine (0.62ml), Pencillin G N-ethyl piperidine salt (0.53g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.382g) added sequentially. After stirring at room temperature for 2h the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and evaporated in vacuo to afford the title compound (0.72g) as an orange foam, ^1H n.m.r. (DMSO-d_6) δ 1.0 - 3.8 (28H), 1.23 (9H), 1.25 (9H), 4.25 (0.5H), 4.42 (0.5H), 4.78 (0.5H), 4.92 (0.5H), 5.3 - 5.6 (2H), 7.1 - 7.6 (5H), 8.1 - 8.5 (1H) and 8.85 (1H), γ_{max} ($CHBr_3$) 3420, 1788, 1668 and 1512cm^{-1}.

Intermediate 36

(4R)-4-[[(1,1-Dimethylethyl)amino]carbonyl]-3-thiazolidinecarboxylic acid, 1,1-dimethylethyl ester

t-Butylamine (1.04ml) was added to a solution of (4R)-3,4-thiazolidinedicarboxylic acid-3-(1,1-dimethylethyl ester)[4] (2.09g), diisopropylethylamine (1.72ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.47g) in dimethylformamide (20ml) and the solution stirred at room temperature under nitrogen for 2hr. The mixture was diluted with ethyl acetate and the solution washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine. The organic phase was separated, dried ($MgSO_4$) and the solvent evaporated in vacuo to afford a solid. Recrystallization from cyclohexane gave the title compound (2.36g), m.p. 128-129°, $[\alpha]_D^{20}$ -142.2° (c 1.05, methanol).

4. G. Perseo, S. Piani and R de Castiglione, Int.J.Peptide Protein Res., 1983, 21, 227.

Intermediate 37

(4R)-N-(1,1-Dimethylethyl)-4-thiazolidinecarboxamide, hydrochloride

6M hydrogen chloride in 1,4-dioxan (10ml) was added to a stirred suspension of Intermediate 36 (2.16g) in 1,4-dioxan (20ml). A solution formed which was stirred at room temperature under nitrogen for 15min. A further quantity of hydrogen chloride in 1,4-dioxan (5ml) was added and the mixture stirred for an additional 3h at room temperature. The precipitated solid was collected by filtration and washed with ether to give the title compound (1.45g), mp. 244-245°, $[\alpha]_D^{19}$ -99.8° (c 1.00, methanol).

Intermediate 38

[2'RS,4''R]-N-[3-[4-[[(1,1-Dimethylethyl)amino]carbonyl]-3-thiazolidinyl]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

A solution of Intermediate 14 (1.0g), Intermediate 37 (0.707g) and diisopropylethylamine (0.7ml) in ethanol (12ml) was stirred at room temperature for 68h under nitrogen. Additional Intermediate 14 (0.52g) in ethanol (5ml) was added and the solution refluxed under nitrogen for 48h. The reaction mixture was cooled and the solvent evaporated in vacuo to an oil which was dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel (Merck Kieselgel 60, 50g) using ethyl acetate/cyclohexane (1:1) to give the title compound (372mg) as a gum which contained both diastereomers, i.r. ($CHBr_3$) γ_{max} 3477, 1705, 1673 and 1509cm^{-1}, ^{1}H n.m.r. (DMSO-d_6) δ 1.25 (9H), 1.38 (9H), 2.2-2.5 (2H), 2.7-3.5 (4H), 3.6 (1H), 3.8-4.15 (3H), 4.85-5.1 (1H), 6.6-6.9 (1H) and 7.45 (1H).

Intermediate 39

[4R,2''RS]-3-(3-Amino-2-hydroxypropyl)-N-(1,1-dimethylethyl)-4-thiazolidinecarboxamide

Intermediate 38 (349mg) in 1,4-dioxan (10ml) was stirred for 20h with 8.5M hydrogen chloride in 1,4-dioxan (2ml). The mixture was concentrated to give the title compound (326mg) as a creamy solid, i.r. (DMSO-d_6) γ_{max} 3700-3250, 1671 and 1515cm^{-1}, ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (9H), 2.5-4.5 (10H + exchangeable protons) and 7.5-8.2 (1H).

Intemediate 40

[2S-[2α(2'R*S*,4''S*)5α,6β]]-3,3-Dimethyl-N-[3-[4-[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinyl]-2-hydroxypropyl]-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide

Intermediate 39 (304mg) was dissolved in N,N-dimethylformamide (16ml) and diisopropylethylamine (540μl), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (356mg) added. After stirring briefly, pencillin G N-ethylpiperidinium salt (456mg) was added and the mixture was stirred for 21h under nitrogen at room temperature. Water was then added and the solution extracted with ethyl acetate. The combined organic fractions were washed with saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and concentrated to a foam before purification by column chromatography on silica gel (Merck Kieselgel 60, 50g) using mixtures of ethyl acetate and methanol (9:1 then 4:1) as eluant to give the title compound (224mg) as a brown foam which contained both stereoisomers, i.r. ($CHBr_3$) γ_{max} 3578, 1791, 1669, 1621 and 1508cm^{-1}, ^{1}H n.m.r. (DMSO-d_6) δ 1.28 (9H), 1.40 (3H), 1.58 (3H), 2.2-2.6 (1H), 2.6-3.2 (2H), 3.2-3.8 (5H), 3.90 (2H), 3.95-4.3 (3H), 5.10 (1H), 5.45 (2H), 7.1-7.5 (6H), 8.16 (1H) and 8.88 (1H).

Intermediate 41

(1'S)-N-[1-(Cyclohexylmethyl)-2-[(1,1-dimethylethyl)amino]-2-oxoethyl]carbamic acid, 9H-fluoren-9-ylmethyl ester

t-Butylamine (0.42ml) was added to a solution of (2S)-α-[[[(9H-fluoren-9-yl-methyl)oxy]carbonyl]amino]cyclohexanepropanoic acid (1.5g), 2-(1H-benzotriazol-1-yl)-1,1-3,3-tetramethyluronium tetrafluoroborate (1.38g), 1-hydroxybenzotriazole hydrate (0.54g) and diisopropylethylamine (0.69ml) in dimethylformamide (15ml) at room temperature. After 17h the solution was diluted with ethyl acetate and washed with water (x3) and saturated sodium hydrogen carbonate solution (x3). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to leave an oil which was purified by silica gel chromatography using 40-60° petrol:ether (2:1) as eluant to afford the title compound (1.14g) as an oil, ^{1}H n.m.r. (DMSO-d_6) δ 0.7 to 1.8 (13H), 1.25 (9H), 4.02 (1H), 4.1 to 4.4 (3H), 7.2-7.5 (6H), 7.75 (2H) and 7.90 (2H), i.r. γ_{max} ($CHBr_3$) 3423, 1710, 1675 and 1508cm^{-1}.

Intermediate 42

(2'S)-α-Amino-N-(1,1-dimethylethyl)-cyclohexanepropanamide

Intermediate 41 (90mg) was dissolved in dimethylformamide (2ml) and piperidine (0.5ml) added. The solution was stirred at room temperature for 2hr and then poured into water. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a white solid. Purification by silica gel column chromatography using chloroform/methanol (20:1) as eluant afforded the title compound, mp. 39-40°, $[\alpha]_D^{23}$ +23.5° (c 0.66, methanol).

Intermediate 43

[2'RS,1''S]-N-[3-[1-(Cyclohexylmethyl)-2-[(1,1-dimethylethyl)amino]-2-oxoethyl]amino-2-hydroxypropyl]carbamic acid,1,1-dimethylethyl ester

Intermediate 42 (50mg) was dissolved in ethanol (2ml) and added to Intermediate 14 (38.3mg). After stirring at room temperature for three days under nitrogen the solvent was evaporated in vacuo. The residue was purified by silica gel chromatography using chloroform/methanol (50:1) as eluant to afford the title compound (64mg) as a colourless oil, ^{1}H n.m.r. (DMSO-d_6) δ 1.28 (9H), 1.5 (9H),

0.7 to 2.0 (14H), 2.3-2.6 (2H), 2.7 to 3.1 (2H), 3.20-3.50 (2H), 4.72 (1H), 6.65 (1H) and 7.45 (1H), i.r. γ_{max} ($CHBr_3$) 3445, 1703, 1660 and 1512cm^{-1}.

Intermediate 44

(4S)-4-(Cyclohexylmethyl)-5-oxo-3-oxazolidinecarboxylic acid, 9H-fluoren-9-ylmethyl ester

Paraformaldehyde (1g) and p-toluenesulphonic acid hydrate (0.1g) were added to a solution of (2S)-α-[[[(9H-fluoren-9-ylmethyl)oxy]carbonyl]amino]-cyclohexanepropanoic acid (1.5g) in toluene (100ml). The mixture was refluxed for 1 h with azeotropic removal of water. The mixture was allowed to cool and then washed with water (3x) and saturated sodium hydrogen carbonate solution (3x). The organic phase was separated, dried (Na_2SO_4) and the solvent evaporated in vacuo to leave an oil (1.78g). Purification by silica gel column chromatography using 40-60° petroleum/ether (1:1) as eluant gave the title compound (1.47g) as an oil, ^1H n.m.r. (DMSO-d_6) δ 0.5 - 0.8 (13H), 3.8 -4.8, 5.20 (1H), 5.32 (1H), 7.2-7.5 (4H), 7.68 (2H) and 7.90 (2H), γ_{max} ($CHBr_3$) 1797, 1709, 1449 and 1419cm^{-1}.

Intermediate 45

(2S)-α-[[[9H-Fluoren-9-ylmethyl)oxy]carbonyl]methylamino]cyclohexanepropanoic acid

Trifluoroacetic acid (15ml) and triethylsilane (1.5ml) were added to a solution of Intermediate 44 in chloroform (15ml) and the mixture stirred 21hr. The solvent was evaporated in vacuo and the residue then purified by silica gel column chromatography using chloroform/methanol/water (180:20:1) as eluant to give the title compound (1.37g), ^1H n.m.r. (DMSO-d_6) δ 0.6 - 1.3 (6H), 1.4 - 1.9 (7H), 2.72 (3H), 2.75 (3H), 4.1 - 4.7 (4H), 7.2 - 7.5 (4H), 7.68 (2H) and 7.9 (2H), γ_{max} ($CHBr_3$) 1712, 1692 and 1450cm^{-1}.

Intermediate 46

)-N-[1-(Cyclohexylmethyl)-2-[(1,1-dimethylethyl)amino]-2-oxoethyl]-N-ylcarbamic acid, (9H-fluorenyl-9-yl-methyl)ester

Diisopropylethylamine (0.47ml), t-butylamine (0.258ml), and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.867g) were added sequentially to a solution of Intermediate 45 (1.0g) in dimethylformamide (20ml) and the mixture stirred at room temperature for 3h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was then washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to a brown oil. Purification by silica gel column chromatography using cyclohexane/ethyl acetate (4:1) as eluant gave the title compound (0.839g) as a white solid, m.p. 136-139°, ^1H n.m.r. (DMSO-d_6) 0.7 - 1.3 (6H), 1.25 (9H), 1.3 - 1.8 (7H), 2.78 (3H), 4.2 - 4.7 (4H), 7.2 - 7.5 (5H), 7.65 (2H) and 7.9 (2H).

Intermediate 47

(2S)-α-(Methylamino)-N-(1,1-dimethylethyl)cyclohexanepropionamide

Piperidine (0.5ml) was added to a solution of Intermediate 46 (0.1g) in dimethylformamide (2ml) and the mixture stirred at room temperature for 1h. The reaction mixture was then partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to give a white solid, which was purified by silica gel column chromatography using chloroform/methanol 30:1 as eluant to give the title compound (0.038g), m.p. 59-61°, $[\alpha]_D^{23}$ +14.5° (c 1.0, CH_3OH).

Intermediate 48

[2'RS,1''S]-N-[3-[[1-(Cyclohexylmethyl)-2-[(1,1-dimethylethyl)amino]-2-oxoethyl]methylamino]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

Intermediate 47 (22mg) was added to a solution of Intermediate 14 (17mg) in ethanol (1ml) and the mixture stirred at room temperature 72h. The solvent was then evaporated in vacuo and the residue purified by silica gel column chromatography using chloroform/methanol 50:1 as eluant to give the title compound (26mg), ^1H n.m.r. (DMSO-d_6) δ 0.6 - 2.0 (13H), 1.25 (9H), 1.38 (9H), 2.32 (3H), 2.35 (3H), 2.2-2.7 (2H), 2.7-3.6 (4H), 3.64 (1H), 4.62 (0.5H), 4.78

(0.5H), 6.70 (0.5H), 7.10 (0.5H), 7.47 (0.5H) and 7.65 (0.5H), γ_{max} ($CHBr_3$), 3445, 1705, 1673 and 1507cm^{-1}.

Intermediate 49

(2S, trans)-4-(1,1-Dimethylethoxy)-1,2-pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester

Di-tert-butyldicarbonate (1.17g) in dioxan (16ml) was added to an ice-cooled solution of (2S-trans)-4-(1,1-dimethylethoxy)-2-pyrrolidinecarboxylic acid (0.84g) in water (12ml) containing 1N sodium hydroxide (8ml) and the mixture stirred at room temperature for 24hr. The reaction mixture was then added to ethyl acetate and the aqueous phase acidified to pH 3.0 with 2N-hydrochloric acid. The ethyl acetate layer was separated, washed with brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to give the title compound (1.25g), m.p. 80-81°, $[\alpha]_D^{23}$ -32.6° (c 1.07, methanol).

Intermediate 50

(2S, trans)-4-(1,1-Dimethylethoxy)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

t-Butylamine (0.46ml), diisopropylethylamine (0.83ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (1.53g) were added sequentially to a solution of Intermediate 49 (1.25g) in dimethylformamide (20ml) and the mixture stirred at room temperature for 17hr. The mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to an orange oil. Purification by silica gel column chromatography using chloroform/methanol 50:1 as eluant afforded the title compound (0.87g), m.p. 135°, $[\alpha]_D^{23}$ -12.06° (c 1.16, methanol).

Intermediate 51

[(2''S, trans)2'RS]-N-[3-[4-(1,1-Dimethylethoxy)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

8.5M Hydrogen chloride in dioxan (1.4ml) was added to a solution of Intermediate 50 (0.78g) in methanol (15ml) and the mixture stirred 17h at room temperature. The solvent was then evaporated in vacuo to yield a white solid (0.62g). The salt was dissolved in ethanol (20ml), and Intermediate 14 and diisopropylethylamine (0.41ml) were added. The reaction was stirred at room temperature for 72h and the solvent then evaporated in vacuo to a yellow oil. Purification by silica gel column chromatography using ethyl acetate/chloroform 75:25 as eluant gave the title compound (0.596g), m.p. 32-38°, ^{1}H n.m.r. δ 1.1 (9H), 1.25 (9H), 1.38 (9H), 1.6 - 1.9 (2H), 2.0 - 2.5 (4H), 2.7 - 3.1 (3H), 3.52 (1H), 4.10 (1H), 4.70 (0.5H), 4.90 (0.5H), 6.68 (1H), 7.26 (0.5H) and 7.55 (0.5H).

Intermediate 52

(2S, cis)-2-[[(1,1-Dimethylethyl)amino]carbonyl]-4-(phenylmethoxyl)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

t-Butylamine (0.6ml), diisopropylethylamine (0.81ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2.0g) were added sequentially to a solution of (2S, cis)-4-(phenylmethoxy)-1,2-pyrrolidinedicarboxylic acid, 1-(1,1-dimethylethyl)ester[5] (1.2g) in dimethylformamide and the mixture stirred at room temperature for 2h. The mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a yellow oil. Purification by silica gel columm chromatography using chloroform/methanol 50:1 as eluant afforded the title compound (1.4g), $[\alpha]_D^{23}$ -15.1° (c 0.63, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (9H), 1.35 (9H), 1.7 - 2.6 (2H), 3.30 (1H), 3.60 (1H), 3.9 - 4.2 (2H), 4.45 (2H), 6.95 (1H) and 7.2 - 7.4 (5H).

5. D.Papaioanniou et al., Acta.Chem.Scand., 1990, 44(3), 243.

Intermediate 53

[2'RS,(2''R, cis)]-N-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

6M Hydrogen chloride in dioxan (4ml) was added to a solution of Intermediate 52 (1.1g) in dioxan (10ml) and the mixture stirred at room temperature for 2h. Evaporation of the solvent in vacuo afforded a yellow foam which was dissolved in ethanol (15ml) and treated with diisopropylethylamine (0.539ml) and Intermediate 14. The mixture was stirred at room temperature for 64hr and the solvent then evaporated in vacuo to leave a gum. Purification by silica gel column chromatography using chloroform/methanol 50:1 as eluant afforded the title compound (0.67g) as a gum, $[\alpha]_D^{23}$ -27.9° (c 1.2, methanol), ^1H n.m.r. (DMSO-d_6) δ 1.22 and 1.21 (9H), 1.38 (9H), 1.80 (1H), 2.20 - 3.50 (8H), 3.58 (1H), 4.40 (2H), 4.05 (1H), 4.72 (0.5H), 4.90 (0.5H), 6.62 (1H), 7.2 - 7.4 (5.5H) and 7.68 (0.5H).

Intermediate 54

[3S-[3α,4αβ,8αβ],2'S,2''S,5''R,6''R]-N-(1,1-Dimethylethyl)-2[3-[[3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo [3.2.0] hept-2-ylcarbonyl]amino]-2-hydroxypropyl]decahydro-3-isoquinolinecarboxamide

Intermediate 15 isomer 2 (750mg) in 1,4-dioxan (20ml) was stirred for 20h with ~8M hydrogen chloride in 1,4-dioxan (3.0ml) under N_2 at room temperature. The mixture was concentrated to a white solid and re-dissolved in dimethylformamide (20ml) to which was added diisopropylethylamine (0.95ml), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (643mg) and penicillin G N-ethyl piperidine salt (815mg). The mixture was stirred at room temperature for 2h, water (100ml) was then added and the solution extracted with ethyl acetate (100ml). The aqueous layer was further washed with ethyl acetate (30ml) and combined organic layers washed with saturated sodium hydrogen carbonate (50ml) and saturated sodium chloride (100ml), dried and evaporated to

give the title compound as an orange oil (1.05g), ^{1}H n.m.r. (DMSO-d_6) δ 1.25 (9H), 1.48 (3H), 1.65 (3H), 1.1 - 2.2 (14H), 2.2 - 3.1 (4H), 3.3 - 3.8 (4H), 4.42 (1H), 4.80 (1H), 5.40 (1H), 5.52 (1H), 7.2 - 7.4 (5H), 7.60 (1H), 8.48 (1H) and 8.90 (1H).

Intermediate 55

(2S)-2-[[(1,1-(Dimethylethyl)amino]carbonyl]-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

A solution containing L-proline, 1,1-dimethylethyl ester (1.5g), 2-(1H)-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2.75g), tert-butylamine (0.74ml) and diisopropylethylamine (1.34ml) in dimethylformamide (25ml) was stirred at room temperature for 20h. The solution was then diluted with water (50ml) and extracted with ethyl acetate (3x50ml). The combined organic extracts were washed with 2N hydrochloric acid (50ml), saturated aqueous sodium bicarbonate (50ml) and brine (50ml), dried ($MgSO_4$) and concentrated in vacuo to a solid which was purified by chromatography on silica gel. Elution with 100:1 chloroform/methanol gave the title compound as a white solid (1.56g), m.p. 119-121R' $[\alpha]_D^{21}$ -47.8° (c 0.98, methanol), ^{1}H n.m.r. ($CDCl_3$) δ 1.35 (9H), 1.47 (9H), 1.87 (2H), 1.9-2.5 (2H), 3.44 (2H), 4.10 (1H) and 5.6-7.0 (1H).

Intermediate 56

[2'RS,2''S]-N-[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

Intermediate 55 (1.0g) was stirred in dioxan (10ml) at room temperature to which was added 3M hydrogen chloride in dioxan (8ml). After 2h the reaction mixture was concentrated to a white foam which was re-dissolved in ethanol (15ml). N-ethyldiisopropylamine (0.71ml) and Intermediate 14 (0.6g) were added and stirring continued for 20h. The reaction mixture was concentrated to an oil and purified by column chromatography on silica gel (Merck 9385, 20g) using a chloroform:methanol (100:1 → 20:1) gradient elution to yield the title compound (407mg) as a 1:1 mixture of diastereoisomers, ^{1}H n.m.r (DMSO-d_6) δ 1.25 (9H),

1.35 (9H), 1.5-1.8 (3H), 1.9-2.6 (3H), 2.6-3.7 (6H), 4.72 (0.5H), 4.94 (0.5H), 6.70 (1H), 7.38 (0.5H) and 7.68 (0.5H).

Intermediate 57

(4R)-5,5-Dimethyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinecarboxylic acid, 1,1-dimethyl ester

A solution containing tert-butoxycarbonyl-L-5,5-dimethylthiazolidine-4-carboxylic acid[6] (2.0g), tert-butylamine (0.89ml), 2-(1H)-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2.95g) and ethyldiisopropylamine (1.47ml) in dimethylformamide (10ml) was stirred at room temperature for 20h and then diluted with water (20ml) and extracted with ethyl acetate (2x20ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (30ml) and brine (30ml), dried ($MgSO_4$) and concentrated in vacuo to an oil which was purified by chromatography on silica gel. Elution with 200:1 chloroform/methanol gave the title compound (0.57g) as a white solid. m.p. 98-101°; $[\alpha]_D^{21}$ -5.9° (c 1.02, methanol), ^1H n.m.r. ($CDCl_3$) δ 1.33 (9H), 1.42 (3H), 1.45 (9H), 1.55 (3H), 3.90 (1H); 4.63 (2H) and 5.76 (1H).

6. J.Samanen et al., J.Med.Chem., 1989, 32(2), 466-472.

Intermediate 58

[2'RS,4''R]-N-[3-[5,5-Dimethyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinyl]-2-hydroxypropyl]carbamic acid, 1,1-dimethylethyl ester

Intermediate 57 (0.8g) was stirred in 1,4- dioxan (10ml) at room temperature to which was added 3M hydrogen chloride in 1,4-dioxan (7ml). After 6h the mixture was concentrated to a white solid which was re-dissolved in ethanol (10ml). N-ethyldiisopropylamine (0.44ml) and Intermediate 14 (0.6g) were added and stirring continued for 72h. The reaction mixture was concentrated to an oil and partitioned between ethyl acetate (30ml) and saturated sodium bicarbonate (20ml). The organic layer was separated, further washed with saturated sodium chloride (20ml) and re-concentrated to an oil (1.2g), which was purified by column

chromatography on silica gel (Merck 9385, 120g) using chloroform:methanol (80:1) to yield both isomers of the title compound. Isomer 1 (175mg), m.p. 98-104° (Slow melt), $[\alpha]_D^{21}$ -177.9° (c 1.01, methanol), Isomer 2 (157mg), m.p. 102-105°, $[\alpha]_D^{21}$ -149.7° (c 0.97, methanol).

Intermediate 59

(4RS)-2,2,5,5-Tetramethyl-N-(1,1-dimethylethyl)-4-thiazolidineacetamide

DL-Penicillamine acetone adduct hydrochloride monohydrate (4.85g) was dissolved in dimethylformamide (100ml) and diisopropylethylamine (5.1g), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (6.4g) and tert-butylamine (2.1ml) added. The solution was stirred for 2h at room temperature. Water (300ml) was then added and the solution extracted with ethyl acetate (2x150ml). The combined organic fractions were then washed with saturated sodium hydrogen carbonate (100ml) and saturated sodium chloride solution (100ml), dried ($MgSO_4$) and concentrated in vacuo to give the title compound (2.0g) as a white solid, m.p. 140°, ^1H n.m.r. (DMSO-d_6), δ 1.18 (3H), 1.28 (9H), 1.42 (3H), 1.50 (3H), 1.58 (3H); 3.2 - 3.4 (1H), 3.62 (1H) and 7.48 (1H).

Intermediate 60

[2''R,4''RS]-N-[2-Hydroxy-3-[2,2,5,5-tetramethyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinyl]propyl]carbamic acid, 1,1-dimethylethyl ester

Intermediate 59 (300mg) was added to Intermediate 68 (500mg) in ethanol (1.5ml) and the mixture was refluxed for 60h. The solvent was evaporated in vacuo and the residue purified by silica gel column chromatography (Merck 9385) using cyclohexane/ethyl acetate (2:1) as eluant to afford the title compound (191mg) as a colourless oil, $[\alpha]_D^{23}$ -22.4° (c 0.49, methanol), ^1H n.m.r. (DMSO-d_6) δ 1.0-1.8 (30H), 2.2-3.8 (6H), 4.4-5.2 (1H), 6.5-6.8 (1H), 7.50 (0.5H) and 7.75 (0.5H).

Intermediate 61

(2RS)-1,2,4-Piperazinetricarboxylic acid,1-(1,1-dimethylethyl ester)-4-(phenylmethyl ester)

A solution containing di tert-butyl pyrocarbonate (8.1g) in 1,4-dioxan (100ml) was added to an ice-cooled solution of (RS)-4-[phenyl[methoxycarbonyl]]piperazine-2-carboxylic acid[7] (1.01g) in 1.0N aqueous sodium hydroxide (150ml). The mixture was stirred for 0.5h and then the ice-bath was removed and stirring was continued for a further 18h at room temperature. The mixture was then concentrated in vacuo to ca. 100ml and the aqueous residue washed with ether (2x100ml). The aqueous extract was then acidified to pH 2 with 2N hydrochloric acid and extracted with ethyl acetate (2x200ml). The combined organic extracts were washed with brine (50ml), dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a pale yellow foam (1.31g). γ_{max} ($CHBr_3$) 1693cm^{-1} (C=O), ^1H n.m.r. (DMSO-d_6) δ 1.39 (9H), 2.7-3.6 (3H + H_2O), 3.72 (1H), 3.90 (1H), 4.3-4.6 (2H), 5.05 (2H) and 7.35 (5H).

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Intermediate 62

(2RS)-2-[[(1,1-Dimethylethyl)amino]carbonyl]-1,4-piperazinedicarboxylic acid,1-(1,1-dimethylethyl ester)-2-(phenylmethyl ester)

2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (1.16g) was added to a solution containing Intermediate 61 (1.06g), tert-butylamine (0.4ml) and diisopropylethylamine (0.6ml) in dimethylformamide (10ml). The solution was stirred at room temperature under nitrogen for 2.5h and was then diluted with ethyl acetate (250ml), washed with 0.5M hydrochloric acid saturated sodium bicarbonate and brine, dried ($MgSO_4$) and evaporated in vacuo to a solid which was crystallised from hot cyclohexane to give the title compound as fine colourless needles (896mg), m.p. 110-111°, γ_{max} ($CHBr_3$) 1686cm^{-1} (C=O), ^1H n.m.r. (DMSO-d_6) δ 1.18 (9H), 1.36 (9H), 2.8-3.7 (4H), 3.86 (1H), 4.0-4.5 (2H), 5.07 (2H), 7.33 (5H) and 7.55 (1H).

Intermediate 63

(3RS)-3-[[(1,1-Dimethylethyl)amino]carbonyl]-1-piperazinecarboxylic acid, phenylmethyl ester, trifluoroacetic acid salt

A solution containing Intermediate 62 (919mg) and trifluoroacetic acid (2ml) in dichloromethane (25ml) was stirred at room temperature for 6h. The solution was evaporated in vacuo to a white solid which was crystallised from chloroform/cyclohexane to give the title compound as colourless needles (513mg), m.p. 91-92°, γ_{max} (nujol) 3296 (NH), 1658cm^{-1} (C=O), ^{1}H n.m.r. (DMSO-d_6) δ 1.28 (9H), 2.9-3.4 (4H), 3.7-4.1 (2H), 4.27 (1H), 5.12 (2H), 7.36 (5H), 8.38 (1H) and 8.9-9.6 (2H).

Intermediate 64

[3RS,2'S]-3-[[(1,1-Dimethylethyl)amino]carbonyl]-4-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxypropyl]-1-piperazinecarboxylic acid, phenylmethyl ester

A solution containing Intermediate 71 (198mg), Intermediate 63 (502mg) and diisopropylethylamine (150mg) in ethanol (5ml) was stirred under an atmosphere of dry nitrogen at room temperature for 6 days. The mixture was then diluted with ethyl acetate (100ml) and the solution washed with brine (50ml), dried ($MgSO_4$) and evaporated in vacuo to an oil which was purified by chromatography on silica gel. Elution with ethyl acetate gave the title compound (340mg) as a pale yellow oil, γ_{max} ($CHBr_3$) 3445 (NH), 1692cm^{-1} (C=O), ^{1}H n.m.r. (DMSO-d_6) δ 1.26 (9H), 1.36 (9H), 2.0 - 2.5 (3H), 2.6 - 3.2 (6H), 3.5 - 4.0 (3H), 4.75 and 4.96 (1H), 5.09 (2H), 6.68 (1H), 7.35 (5H) and 7.53 (1H).

Intermediate 65

[3RS,2'S]-3-[[(1,1-Dimethylethyl)amino]carbonyl]-4-(3-amino-2-hydroxypropyl)-1-piperidinecarboxylic acid, phenylmethyl ester, trifluoroacetic acid salt

A solution containing Intermediate 64 (308mg) and trifluoroacetic acid (2ml) in dichloromethane (10ml) was stirred at room temerature for 2h and was then evaporated to dryness in vacuo. The residual oil was triturated with ether to give

the title compound as a white powder (213mg), γ_{max} (Nujol) 1671cm^{-1} (C=O), ^{1}H n.m.r. (DMSO-d_6) δ 1.29 (9H), 2.5 - 3.5 (9H), 3.7 - 4.1 (3H), 5.11 (2H), 7.38 (5H) and 7.8 - 8.3 (4H).

Intermediate 66

(2'R)-N-(2,3-Dihydroxypropyl)carbamic acid, dimethylethyl ester

A solution containing (S)-glycidol (5.0ml) in saturated ammoniacal isopropanol (1250ml) was stirred at room temperature for 67h and was then evaporated in vacuo. The residual oil was dissolved in 1,4-dioxan (250ml) and 0.5N aqueous sodium hydroxide (250ml) and treated with di-tert-butylpyrocarbonate (18.5g) at room temperature for 20h. The mixture was then concentrated in vacuo to ca. 200ml and the residue saturated with sodium chloride, neutralised to pH 7.0 with 2N hydrochloric acid and then extracted with ethyl acetate (2x300ml). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the title compound as a colourless oil, $[\alpha]_D^{21}$ +11.02° (c 1.62, methanol), γ_{max} ($CHBr_3$) 3444 (NH,OH), 1693cm^{-1} (C=O), ^{1}H n.m.r. (DMSO-d_6) δ 1.36 (9H), 2.92 (2H), 3.45 (1H), 4.49 (1H), 4.66 (1H), and 6.62 (1H).

Intermediate 67

(2'R)-N-[2-[[(4-Methylphenyl)sulphonyl]oxy]-2-hydroxyethyl]carbamic acid,1,1-dimethylethyl ester

A solution containing Intermediate 66 (11.77g) and tosyl chloride (13.14g) in pyridine (60ml) was stirred at room temperature for 18h. The solution was then diluted with ethyl acetate (1200ml) and washed with 2N hydrochloric acid (2x200ml), saturated aqueous sodium bicarbonate (2x200ml) and brine (100ml), dried ($MgSO_4$) and evaporated in vacuo. The residual oil was purified by chromatography on silica gel eluting with 1:1 cyclohexane/ethyl acetate to give the title compound as a viscous oil (16.58g), $[\alpha]_D^{21}$ +11.8° (c 2.58, methanol), ^{1}H n.m.r. ($CDCl_3$) δ 1.44 (9H), 2.46 (3H), 3.1 - 3.6 (3H), 3.8 - 4.1 (3H), 4.91 (1H), 7.36 (2H) and 7.80 (2H).

Intermediate 68

(2'R)-N-(2-Oxiranylmethyl)carbamic acid,1,1-dimethylethyl ester

A solution containing Intermediate 67 (14.77g) and sodium methoxide (4.62g) in methanol (150ml) was stirred at room temperature for 1.5h and then evaporated to dryness in vacuo. The residual solid was partitioned between ethyl acetate (300ml) and water (225ml) and the organic extract washed with brine (50ml), dried ($MgSO_4$) and evaporated in vacuo. The residual oil was purified by chromatography on silica gel. Elution with 4:1 cyclohexane/ethyl acetate gave the title compound as a viscous oil (5.24g), $[\alpha]_D^{21}$ +12.55° (c 2.58, methanol), ^1H n.m.r. ($CDCl_3$) δ 1.43 (9H), 2.60 (1H), 2.80 (1H), 3.1 - 3.4 (2H), 3.55 (1H) and 3.74 (1H).

Intermediate 69

(2'S)-N-(2,3-Dihydroxypropyl)carbamic acid,1,1-dimethylethyl ester

A solution containing (R)-glycidol (1.0ml) in saturated ammoniacal isopropanol (250ml) was allowed to stand at room temperature for 2 days and then the solvent was evaporated in vacuo. The residual oil was taken up in a mixture of 1,4-dioxan (50ml) and 0.5N aqueous sodium hydroxide (50ml) and treated with di-tert-butylpyrocarbonate (3.7g) at room temperature for 20h. The mixture was concentrated in vacuo to approximately half volume and the aqueous residue saturated with sodium chloride, neutralised to pH 7.0 with 2N hydrochloric acid and extracted with ethyl acetate (3x150ml). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to a colourless oil. The oil was purified by chromatography on silica gel eluting with ethyl acetate to give the title compound as a colourless oil (2.1g), $[\alpha]_D^{21}$ -12.1° (c 1.0, $CHCl_3$), γ_{max} ($CHBr_3$) 3444 (NH,OH), 1693cm^{-1} (C=O), ^1H n.m.r. (DMSO-d_6) δ 1.36 (9H), 2.92 (2H), 3.28 (2H), 3.45 (1H), 4.49 (1H), 4.66 (1H) and 6.62 (1H).

Intermediate 70

(2'S)-N-[2-[[(4-Methylphenyl)sulphonyl]oxy]-2-hydroxyethyl]carbamic acid,1,1-dimethylethyl ester

A solution containing Intermediate 69 (257mg) and tosylchloride (286mg) in pyridine (5ml) was stirred at room temperature for 3h. The solution was then diluted with ethyl acetate (100ml) and washed with 0.5N hydrochloric acid (2x50ml), saturated aqueous sodium bicarbonate (3x50ml) and brine (50ml), dried ($MgSO_4$) and then solvent was evaporated in vacuo. The residual oil was purified by chromatography on silica gel eluting with 1:1 ethyl acetate/cyclohexane to give the title compound as a colourless oil (289mg), γ_{max} ($CHBr_3$) 3442 (NH), 1705 (C=O), 1366cm^{-1} (S=O), ^{1}H n.m.r. (DMSO-d_6) δ 1.32 (9H), 2.41 (3H), 2.88 (2H), 3.36 (1H), 3.64 (1H), 3.76 (1H), 3.95 (1H), 6.80 (1H), 7.46 (2H) and 7.79 (2H).

Intermediate 71

(2'S)-N-(2-Oxiranylmethyl)carbamic acid,1,1-dimethylethyl ester

A solution containing Intermediate 70 (229mg) and sodium methoxide (56mg) in methanol (5ml) was stirred at room temperature for 3h and was then evaporated to dryness in vacuo. The residual solid was partitioned between ethyl acetate (100ml) and water (50ml) and the organic extract was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$) and evaporated in vacuo to a colourless syrup. This was purified by chromatography on silica gel eluting with 7:3 cyclohexane/ethyl acetate to give the title compound as a colourless oil (86mg), $[\alpha]_D^{21}$ -14.2° (c 1.01, methanol), γ_{max} ($CHBr_3$) 3443 (NH), 1706 (C=O), 1250cm^{-1} (epoxide), ^{1}H n.m.r. (DMSO-d_6) δ 1.38 (9H), 2.4-2.6 (1H+DMSO), 2.66 (1H), 2.9-3.2 (3H) and 7.00 (1H).

Example 1

[2R-[2α(R*),4β(R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-(2-phenyl-1-hydroxymethyl)ethyl]amino]carbonyl]-2-thiazolidineacetamide

A stirred solution of [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (883mg) and 1-hydroxybenzotriazole monohydrate (337mg) in tetrahydrofuran

(15ml) and dimethylformamide (40ml) was treated with a solution of (R)-phenylalaninol (303mg) in dimethylformamide (2ml) followed by N,N-dicyclohexylcarbodiimide (454mg) and the mixture was stirred at 20° for 5½ hours. The tetrahydrofuran was removed in vacuo and the suspension obtained was filtered. The filtrate was partitioned between ethyl acetate (50ml) and water (160ml). The organic phase was washed successively with water, 2N hydrochloric acid, water and saturated brine. The dried ($MgSO_4$) solution was evaporated to a white solid which was chromatographed on silica gel (Merck 9385, 80g). Elution with chloroform : methanol mixtures varying from 50:1 to 40:1 gave a product as a white powder which crystallised from dichloromethane/ di-isopropyl ether to afford the title compound as a white solid (250mg), mp. 83-86°, $[\alpha]_D^{20}$ +87.8° (C=1.02 in MeOH), ^1H n.m.r. (DMSO-d_6) δ 1.05 (3H), 1.50 (3H), 2.78 (2H), 3.45 (1H), 3.50 (2H), 3.75 (1H), 4.00 (1H), 4.25 (2H), 4.40 (2H), 4.80 (1H), 4.90 (1H), 7.10-7.30 (15H), 7.70 (1H), 8.30 (1H), 8.50 (1H).

Example 2

[2R-[2α(R*),4β]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[1-[1-(hydroxymethyl)pentyl]amino]carbonyl]-2-thiazolidineacetamide

(±)-2-Amino-1-hexanol (175μl) was added to a solution of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.44g), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.6g) and diisopropylethylamine (0.26μl) in dimethylformamide (12ml) under nitrogen. After stirring at room temperature for 17h the reaction mixture was partititoned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined extracts washed with 1N-hydrochloric acid, saturated sodium bicarbonate solution and brine. The ethyl acetate solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a white foam, which was purified by silica gel column chromatography using chloroform/methanol 40:1 to 30:1 as eluant to give the title compound (0.24g), mp. 155-159^0, $[\alpha]_D^{20}$ = +48.5° (C=0.87 in methanol), ^1H n.m.r. (DMSO-d_6) δ 0.95 (3H), 1.25 (3H), 1.58 (3H),

1.8-1.2 (6H), 3.7-3.3 (5H), 4.0-3.7 (2H), 4.6-4.2 (3H), 4.75 (1H), 5.00 (1H), 7.4-7.1 (10H), 7.70 (1H), 8.41 and 8.52 (each 1H).

Example 3

[2R-[2α(R*),4β(R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-ethyl-4-[[[1-(2-phenyl-1-hydroxymethyl)ethyl]amino]carbonyl]-2-thiazolidineacetamide

A solution of N,N-dicyclohexylcarbodiimide (150mg) in dimethylformamide (1ml) was added to a stirred solution of Intermediate 8 (0.25g), (R)-phenylalaninol (100mg) and 1-hydroxybenzotriazole hydrate (111mg) in dimethylformamide (1.5ml). After 6 hours the resulting mixture was filtered and the filtrate was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over magnesium sulphate and then evaporated to a syrup. Purification by chromatography on silica-gel, with elution by mixtures of ethyl acetate and methanol (1:0 to 20:1) gave the title compound as a white foam (177mg, $[\alpha]_D^{20}$ +97° (c 0.99, methanol); ν_{max} ($CHBr_3$) 3393 + 3321 (NH, OH), 1651 (C=O), 1517cm^{-1} (NH); ^1H n.m.r. (DMSO-d_6) δ 0.98 (3H), 1.05 (3H), 1.47 (3H), 2.9-2.6 (2H), 3.04 (2H), 3.4-3.2 (2H), 3.42 (1H), 3.50 (2H), 3.75 (1H), 4.05-3.9 (1H), 4.28 (1H), 4.9-4.7 (2H), 7.32-7.1 (10H), 7.68 (1H), 7.96 (1H), 8.26 (1H).

Example 4

[2R-[2α(R*),4β(R*)]]-5,5-Dimethyl-α-[[(4-fluorophenyl)acetyl]amino]- N-(2-pyridinylmethyl)-4-[[[1-(2-phenyl-1-hydroxymethyl)ethyl]amino]carbonyl]-2-thiazolidineacetamide

To a stirred solution of Intermediate 7 (0.78g) in dimethylformamide (14ml) was added (R)-phenylalaninol (0.257g), diisopropylethylamine (326μl) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.6g). After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic layers washed with 1N-hydrochloric acid. The acid extract was then adjusted to pH 8.0 with potassium carbonate and re-extracted with ethyl

acetate. The organic extract was dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a yellow oil (0.74g). Purification by silica gel column chromatography using dichloromethane/methanol 30:1 to 10:1 as eluant gave the title compound (0.2g), mp. 77-80°, $[\alpha]_D^{20}$ = -70.5° (C=0.78 in methanol), ^1H n.m.r. (DMSO-d_6) δ 1.05 (3H), 1.50 (3H), 3.0-2.6 (2H), 3.54 (1H), 3.7-3.3 (4H), 3.80 (1H) and 4.04 (1H).

Example 5

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[2-hydroxy-4-[1-(2-methylpropyl)amino]]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-thiazolidineacetamide

3.3M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 5 (0.2g) in 1,4-dioxan (4ml) at room temperature. After 2.5h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (4ml) and diisopropylethylamine (400μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.19g) added. After stirring at room temperature for 16h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a brown solid (0.46g). Purification by silica gel column chromatography using chloroform/methanol 50:1 to 30:1 as eluant gave the title compound (0.16g), mp. 176-178°, $[\alpha]_D^{20}$ = +86.0° (C=0.44 in DMSO), ^1H n.m.r. (DMSO-d_6) δ 0.68 (6H), 1.08 (3H), 1.50 (3H), 1.62 (1H), 2.4-2.0 (2H), 3.0-2.5 (4H), 3.7-3.4 (3H), 4.1-3.8 (3H), 4.4-4.1 (2H), 4.45 (1H), 4.86 (1H), 5.22 (1H), 7.4-7.1 (15H), 7.58 (1H), 8.33 (1H), 7.75 (1H) and 8.50 (1H).

Example 6

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[1-[3-(aminocarbonyl)-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-thiazolidineacetamide

3M-Hydrogen chloride in 1,4-dioxan (2.5ml) was added to Intermediate 12 (0.15g) in 1,4-dioxan (20ml) at room temperature. The solution was stirred for 15h and the solvent then removed in vacuo to afford a white solid. This was dissolved in dimethylformamide (4ml) and diisopropylethylamine (114μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino] ethyl]-4-thiazolidinecarboxylic acid (0.17g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.14g) added. After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with saturated sodium hydrogen carbonate solution and dried ($MgSO_4$). The solvent was evaporated in vacuo to low volume and then cooled to 4° to give crystals. Recrystallisation from ethyl acetate afforded the title compound (45mg), mp. 167-168°, $[\alpha]_D^{20}$ = +90.0° (C=0.25 in DMSO), ^{1}H n.m.r. (DMSO-d_6) δ 1.05 (3H), 1.50 (3H), 2.3-2.0 (2H), 3.0-2.6 (2H), 3.7-3.3 (3H), 4.5-3.8 6H), 4.86 (1H), 5.26 (1H), 6.84 (1H), 7.4-7.2 (16H), 7.60 (1H), 8.35 (1H) and 8.53 (1H).

Example 7

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[2-hydroxy-4-[[(1H-benzimidazol-2-yl) methyl]amino]-4-oxo-1-(phenylmethyl)]butyl]amino]carbonyl]-2-thiazolidineacetamide

3.2M hydrogen chloride in 1,4-dioxan (5ml) was added to a solution of Intermediate 4 (0.2g) in 2:1 methanol : chloroform (20ml). The mixture was stirred at room temperature for 18h and the solvent then evaporated in vacuo to give the amine hydrochloride as a yellow solid. The amine hydrochloride was dissolved in dimethylformamide (5ml) and diisopropylethylamine (131μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.2g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.15g) added. After stirring at room

temperature for 18h the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow oil. Purification by silica gel chromatography using chloroform/methanol (50:1) as eluant afforded the title compound (0.17g) as a white solid, mp. 136-139°, $[\alpha]_D^{20}$ = +82.4° (C=0.51 in methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.09 (3H), 1.53 (3H), 2.1-2.45 (2H), 2.73 (1H), 2.92 (1H), 3.6-3.35 (3H), 4.6-3.8 (8H), 4.88 (1H), 5.48 (1H), 7.45 (2H), 7.35-7.1 (17H), 7.75 (1H), 8.40 (1H) and 8.52 (2H).

Example 8

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[2-hydroxy-4-[(phenylmethyl)amino]-4-oxo-1-(phenylmethyl)]butyl]amino]carbonyl]-2-thiazolidineacetamide

3.2M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 3 (0.2g) in 1,4-dioxan (3ml). The mixture was stirred at room temperature for 3h and the solvent then evaporated in vacuo to give the amine hydrochloride as a yellow foam. The amine hydrochloride was dissolved in dimethylformamide (5ml) and diisopropylethylamine (193μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.24g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.16g) added. After stirring at room temperature for 18h the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with 2N-hydrochloric acid saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to a brown oil. Purification by flash silica column chromatography using chloroform/methanol (50:1) as eluant gave the title compound (0.12g) as a solid, mp. 98-101°, $[\alpha]_D^{20}$ = +80.4° (C=0.51 in methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.09 (3H), 1.53 (3H), 2.1-2.45 (2H), 3.0-2.5 (2H), 3.6-3.35 (3H), 4.6-3.8 (8H), 4.88 (1H), 5.32 (1H), 7.45-7.1 (15H), 7.68 (1H), 8.38 (2H) and 8.58 (1H).

Example 9

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[[[1,1'-biphenyl]-2-ylcarbonyl]amino]-N-ethyl-4-[[[1-[2-hydroxy-4-[1-(2-methylpropyl) amino]-4-oxo-1-(phenylmethyl)]butyl]amino]carbonyl]-2-thiazolidineacetamide

3.3M Hydrogen chloride in 1,4-dioxan (15ml) was added to a solution of Intermediate 5 (1.08g) in 1,4-dioxan (20ml) at room temperature. After 2.5h the solvent was evaporated in vacuo to give the hydrochloride salt. A portion of the hydrochloride salt (0.3g) was dissolved in dimethylformamide (10ml) and diisopropylethylamine (364μl), Intermediate 10 and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.35g) added. After stirring at room temperature for 18h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 1N-hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow solid. Purification by silica gel column chromatography using chloroform/methanol 40:1 as eluant gave a solid which was recrystallised from chloroform/methanol (1:1) by the addition of ether to give the title compound (0.11g), mp. 223-225°, $[\alpha]_D^{20}$ = +66.7° (C=1.05 in methanol), ^1H n.m.r. (DMSO-d_6) δ 0.68 (6H), 1.0 (3H), 1.09 (3H), 1.52 (3H), 1.7-1.4 (1H), 2.4-2.0 (2H), 3.2-2.5 (6H), 3.56 (1H), 4.1-3.8 (3H), 4.35 (1H), 4.80 (1H), 5.30 (1H), 8.40 (1H), 7.9-7.7 (3H) and 7.6-7.1 (14H).

Example 10

[2R-[2α(R*),4β(R*,R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-[4-(dimethylaminophenyl)methyl]-4-[[[1-[2-hydroxy-4-[1-(2-methylpropyl)amino]-4-oxo-1-(phenylmethyl)]butyl]amino]carbonyl]-2-thiazolidineacetamide

3.3M Hydrogen chloride in 1,4-dioxan (15ml) was added to a solution of Intermediate 5 (1.08g) in 1,4-dioxan (20ml) at room temperature. After 2.5h the solvent was evaporated in vacuo to give the hydrochloride salt. A portion of the hydrochloride salt (0.33g) was dissolved in dimethylformamide (10ml) and diisopropylethylamine (405μl), Intermediate 9 and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.39g) added. After stirring at room

temperature for 16h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 1N-hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The acid extract was basified to pH8 with potassium hydrogen carbonate to give a white solid which was removed by filtration. The white solid was purified by silica gel chromatography using chloroform/methanol 40:1 as eluant to give the title compound (0.5g) as a white solid mp. 119-121°, $[\alpha]_D^{20}$ = +60.4° (C=0.61 in $CHCl_3$), 1H n.m.r. (DMSO-d_6) δ 0.82 (6H), 1.05(3H), 1.50 (3H), 1.7-1.5 (1H), 2.3-2.1 (2H), 3.0-2.5 (4H), 2.85 (6H), 3.6-3.2 (3H), 4.3-3.7 (5H), 4.43 (1H), 4.85 (1H), 5.26 (1H), 6.65 (2H), 7.03 (2H), 7.4-7.1 (10H), 7.60 (1H), 7.80 (1H) and 8.35 (2H).

Example 11

[2R-[2α(R*),4β(2'S*,3''S*,4a''S*,8a''R*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[2-hydroxy-3-[3-[[(1,1-dimethylethylamino]carbonyl]-decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-2-thiazolidineacetamide

Intermediate 15 (89mg; Isomer 2)in 1,4-dioxan (3ml) was stirred for 20h with 3.3M hydrogen chloride in 1,4-dioxan (1ml). The solvent was evaporated in vacuo to leave a white solid which was dissolved in dry dimethylformamide (3ml) and diisopropylethylamine (113μl), [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.095g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.076g) added. After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic extracts washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and evaporated in vacuo to an orange oil. Purification by silica gel column chromatography (Merck 9385, 26g) using chloroform/methanol (50:1) as eluant gave the title compound (50mg) as a white solid, mp. 115-120° (softens), $[\alpha]_D^{20}$ = -4.55 (C=0.88 in MeOH), ^{1}H n.m.r. (DMSO-d_6) δ 1.6-2.0 (2H), 1.15 (3H), 1.28

(9H), 1.58 (3H), 2.05 (2H), 2.2-2.7 (2H), 2.7-3.0 (2H), 3.4-3.8 (3H), 3.55 (2H), 3.95 (1H), 4.1-4.5 (3H), 4.72 (1H), 7.1-7.4 (11H), 7.98 (1H), 8.3-8.55 (2H).

Example 12

[2R-[2α(R*),4β(S*,R*,S*)]]-5,5-Dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[2-hydroxy-3-[2-[[(1,1-dimethylethyl)amino] carbonyl] piperidin-1-yl]propyl]amino]carbonyl]-2-thiazolidineacetamide

Intermediate 17 (129mg; Isomer 2) in 1,4-dioxan (5ml) was stirred for 20h under nitrogen with 3.3M hydrogen chloride in 1,4-dioxan (2.3ml). The mixture was concentrated to a white solid and re-dissolved in dry dimethylformamide (5ml). The solution was stirred and treated with N-ethyldiisopropylamine (0.19ml), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (127mg) and [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (160mg) for 20h under nitrogen at room temperature. Water (10ml) was then added and the solution extracted with ethyl acetate (3 x 10ml). The combined organic fractions were then washed with saturated sodium hydrogen carbonate (10ml) and saturated sodium chloride solution (10ml), dried and evaporated to a yellow foam. This was purified by column chromatography on silica gel (Merck 9385, 65g) using chloroform : methanol (30:1) to give the title compound as a white solid (112mg), mp. 90-105° (softens), $[\alpha]_D$+18.75° (c 0.96 in MeOH), ^{1}H n.m.r. (DMSO-d_6) δ 1.1-1.7 (6H), 1.24 (9H), 1.18 (3H), 1.50 (3H), 1.98 (1H), 2.14 (1H), 2.38 (1H), 2.58 (1H), 3.10 (2H), 3.51 (1H), 3.50 (2H), 3.68 (1H), 4.25 (2H), 4.42 (1H), 4.80 (1H), 4.90 (1H), 7.25 (11H), 7.97

Example 13

[2R-[2α(R*),4β(R*,R*,R*)]]-5,5-Dimethyl-4-[[[2-hydroxy-4-oxo-4-[1-(hydroxymethyl)-2-phenylethyl]-1-(phenylmethyl)butyl]amino]carbonyl]-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

3M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 18 (200mg) in 1,4-dioxan (3ml) at room temperature. After 2h the

solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (5ml) and diisopropylethylamine (183μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (232mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (156mg)were added sequentially. After stirring at room temperature for 16h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow oil. Purification by silica gel column chromatography using chloroform : methanol 40:1 as eluant gave the title compound (183mg), mp. 101-104°, softens $[\alpha]_D^{23}$ 63.8° (c 0.58, methanol), ^1H n.m.r. ($DMSO_6$) δ 1.08 (3H), 1.49 (3H), 1.9-2.3 (2H), 2.3-3.0 (4H), 3.5-3.65 (3H), 3.7-4.1 (4H), 4.1-4.5 (2H), 4.43 (1H), 4.72 (1H), 4.86 (1H), 5.17 (1H), 7.1-7.35 (20H), 7.60 (1H), 7.68 (1H), 8.29 (1H) and 8.48 (1H).

Example 14

[2R-[2α(R*),4β(R*,R*,R*)]]-5,5-Dimethyl-4-[[[2-hydroxy-4-oxo-4-[1-(hydroxymethyl)-2-phenylethyl]-1-(phenylmethyl)butyl]amino]carbonyl]-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

3M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 19 (150mg) in 1,4-dioxan (2ml) at room temperature. After 2h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (5ml) and diisopropylethylamine (130μl), [2R-[2α(R*),4β]]-5,5,dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (165mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (110mg) were added sequentially. After stirring at room temperature for 16h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 2N hydrochloric

acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow oil. Purification by silica gel column chromatography using chloroform : methanol (40:1) as eluant gave the title compound (143mg), mp. 98-102° softens, $[\alpha]_D^{23}$ +95.2° (c 0.63, methanol), ^1H n.m.r. ($DMSO_6$) δ 1.08 (3H), 1.49 (3H), 2.0-2.2 (2H), 2.4-3.0 (4H), 3.4-3.7 (3H), 3.86 (3H), 4.02 (1H), 4.1-4.5 (2H), 4.43 (1H), 4.69 (1H), 4.86 (1H), 5.17 (1H), 7.1-7.4 (20H), 7.5-7.7 (2H), 8.29 (1H) and 8.48 (1H).

Example 15

[2R-[2α(R*),4β(R*,R*,S*)]]-4-[[[2-Hydroxy-4-[[[(2-hydroxy-1-phenyl)ethyl]amino]carbonyl]-1-(phenylmethyl)-butyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

3M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 20 (200mg) in 1,4-dioxan (4ml) at room temperature. After 2h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissoved in dimethylformamide (5ml) and diisopropylethylamine (189μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (240mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (160mg) were added sequentially. After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solution evaporated in vacuo to give a yellow oil. Purification by silica gel column chromatography using chloroform : methanol (40:1) as eluant gave the title compound (142mg), mp. 110-114°, $[\alpha]_D^{23}$ +87.1° (c 0.62, methanol), ^1H n.m.r. ($DMSO_6$) δ 1.06 (3H), 1.49 (3H), 2.1-2.4 (2H), 2.6-2.95 (2H), 3.4-3.65 (5H), 3.7-4.0 (2H), 4.02 (1H), 4.1-4.5 (2H), 4.42 (1H), 4.7-5.0 (3H), 5.21 (1H), 7.1-7.4 (20H), 7.62 (1H), 8.20 (1H), 8.30 (1H) and 8.50 (1H).

Example 16

[2R-[2α(R*),4β(R*,R*,R*)]]-4-[[[2-Hydroxy-4-[[[(2-hydroxy-1-phenyl)ethyl]amino]carbonyl]-1-(phenylmethyl)butyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

3M Hydrogen chloride in 1,4-dioxan (3ml) was added to a solution of Intermediate 21 (165mg) in 1,4-dioxan (4ml) at room temperature. After 2h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (5ml) and diisopropylethylamine (156μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (198mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (132mg) were added sequentially. After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow oil. Purification by silica gel column chromatography using chloroform : methanol (40:1) as eluant gave the title compound (123mg), mp. 114-117°, $[\alpha]_D^{23}$ +48.0° (c 0.52, methanol), ^1H n.m.r. ($DMSO_6$) δ 1.08 (3H), 1.50 (3H), 2.1-2.4 (2H), 2.6-3.0 (2H), 3.4-3.7 (5H), 3.8-4.0 (2H), 4.05 (1H), 4.1-4.4 (2H), 4.45 (1H), 4.7-5.0 (3H), 5.21 (1H), 7.1-7.4 (20H), 7.61 (1H), 8.14 (1H), 8.32 (1H) and 8.50 (1H).

Example 17

[2R-[2α(R*),4β(R*,R*)]]-4-[[[4-[(2,3-Dihydroxypropyl)amino]-2-hydroxy-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

3M Hydrogen chloride in 1,4-dioxan (4ml) was added to a solution of Intermediate 22 (210mg) in 1,4-dioxan (10ml) at room temperature. After 4.5h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (5ml) and diisopropylethylamine (145μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-

[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (235mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (188mg) were added sequentially. After stirring at room temperature for 1.5h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow solid (303mg). Purification by silica gel column chromatography using chloroform : methanol (40:1 to 10:1) as eluant gave the title compound (61mg), mp. 94-96°, $[\alpha]_D^{23}$ +89.4° (c 1.0, methanol), ^1H n.m.r. ($DMSO_6$) δ 1.08 (3H), 1.50 (3H), 2.0-2.4 (2H), 2.55-3.1 (3H), 3.1-3.7 (7H), 3.7-4.1 (3H), 4.1-4.6 (4H), 4.68 (1H), 4.87 (1H), 5.21 (1H), 7.1-7.4 (15H), 7.60 (1H), 7.74 (1H), 8.30 (1H) and 8.48 (1H).

Example 18

[2R-[2α(R*),4β(S*,S*]]-4-[[[2-Hydroxy-4-[(3-hydroxypropyl)amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

8M Hydrogen chloride in 1,4-dioxan (2ml) was added to a solution of Intermediate 23 (228mg) in 1,4-dioxan (10ml) at room temperature. After 3h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (10ml) and diisopropylamine (221μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (267mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (213mg) were added. After stirring at room temperature for 1h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a yellow oil. Purification by silica gel column chomatography using chloroform : methanol (40:1) as eluant gave the title compound (110mg), mp. 97-101°, $[\alpha]_D^{23}$ +85.9° (c 1.1, methanol).

^{1}H n.m.r. ($DMSO_6$) δ 1.08 (3H), 1.4-1.6 (2H), 1.50 (3H), 2.0-2.3 (2H), 2.55-2.95 (2H), 2.95-3.2 (2H), 3.2-3.4 (2H), 3.45-3.65 (3H), 3.8-4.1 (3H), 4.1-4.5 (4H), 4.88 (1H), 5.20 (1H), 7.1-7.3 (15H), 7.58 (1H), 7.75 (1H), 8.31 (1H) and 8.49 (1H).

Example 19

[2R-[2α(R*),4β[R*,R*]]]-4-[[[2-Hydroxy-4-[[2-(1H-imidazol-2-yl)ethyl]amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

8M Hydrogen chloride in 1,4-dioxan (2ml) was added to a solution of Intermediate 24 (164mg) in a mixture of 1,4-dioxan and methanol (10ml). After 2.5h the solvent was evaporated in vacuo to give the hydrochloride salt. The salt was dissolved in dimethylformamide (5ml) and diisopropylethylamine (220μl), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (180mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (144mg) were added. After stirring at room temperature for 2h the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with saturated sodium hydrogen carbonate solution and brine. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give a brown oil. Purification by silica gel column chomatography using chloroform:methanol (30:1 to 8:1) as eluant gave the title compound (79mg) as a white solid, mp. 172-176°, $[\alpha]_D^{23}$ +77.1° (c 1.1, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.10 (3H), 1.51 (3H), 2.3-2.4 (2H), 2.4-2.8 (3H), 2.8-3.0 (1H), 3.1-3.6 (5H), 3.75-4.1 (3H), 4.1-4.45 (2H), 4.45 (1H), 4.88 (1H), 5.33 (1H), 6.78 (1H), 7.1-7.4 (15H), 7.49 (1H), 7.61 (1H), 7.88 (1H), 8.33 (1H), 8.52 (1H), and 11.77 (1H).

Example 20

[2R-[2α(R*),4β(1R*,2R*)]]-N-Ethyl-4-[[[2-hydroxy-4-oxo-1-(phenylmethyl)-4-[(phenylmethyl)amino]butyl]amino]carbonyl]-5,5-dimethyl-α-[[[[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-thiazolidineacetamide

3.2M Hydrogen chloride in 1,4-dioxan (3.5ml) was added to a solution of Intermediate 3 (0.22g) in 1,4-dioxan (3ml) at room temperature. The solution was stirred at room temperature for 3h and the solvent removed in vacuo to afford a yellow oil. The oil was dissolved in dimethylformamide (5ml) and diisopropylethylamine (106μl), Intermediate 10 (0.134g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.096g) added. After stirring at room temperature for 18h the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, and dried ($MgSO_4$). The solvent was evaporated in vacuo to afford an oil which was purified by silica gel chomatography using chloroform/methanol 40:1 as eluant to give the title compound (63mg), mp. 170-172°, $[\alpha]_D^{23}$ +72.2° (c 0.54, CH_3OH), ^1H n.m.r. (DMSO-d_6) δ 0.99 (3H), 1.08 (3H), 1.52 (3H), 2.1-2.4 (2H), 2.6-3.2 (4H), 3.58 (1H), 3.7-4.4 (6H), 4.82 (1H), 5.30 (1H), 7.1-7.6 (19H), 7.75 (2H), and 8.25-8.45 (2H).

Example 21

[2R-[2α(R*),4β(R*)]]-4-[[[2-Hydroxy-3-[[(1-oxo-2-phenyl)ethyl]amino]-1-(phenylmethyl)propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

Intermediate 30 (280mg) was dissolved in N,N-dimethylformamide (10.5ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (320mg) and N-diisopropylethylamine (200μl) added. After stirring at room temperature for 18h, the mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and evaporated to a foam. Purification by column chomatography on silica gel (Merck Kieselgel 60, 100g) using dichloromethane/methanol (9:1) as eluant gave the title compound (150mg) as a brown foam, $[\alpha]_D^{20}$ +55.6° (c 0.50,DMSO), ^1H n.m.r. (DMSO-d_6) δ 0.93-1.02 (3H), 1.45-1.5 (3H), 2.4-3.1 (5H), 3.1-3.9 (6H), 4.0 (1H), 4.1-4.5 (3H), 4.85 (1H), 5.0-5.5 (1H), 7.0-7.4 (20H) and 7.4-8.6 (4H).

Example 22

[2R-[2α(R*),4β[2'R*S*,3''S*]]]-4-[[[2-Hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]-1,2,3,4-tetrahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

Intermediate 34 (297mg) was dissolved in N,N-dimethylformamide (14ml) and diisopropylethylamine (460μl), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (305mg) and [2R-(2αR*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethylamino]ethyl]-4-thiazolidinecarboxylic acid (384mg) added. After stirring at room temperature for 22h the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium hydrogen carbonate and saturated sodium chloride solution, dried and evaporated to a brown foam. Purification by column chomatography on silica gel (Merck Kieselgel 60, 50g) using dichloromethane/methanol (9:1) as eluant gave the title compound (207mg) as a light brown foam, $[\alpha]_D^{20}$ +49.5° (c 0.55, DMSO), ^{1}H n.m.r. (DMSO-d_6) δ 1.0-1.2 (3H), 1.2-1.3 (9H), 1.3-1.6 (3H), 2.2-2.6 (2H), 2.8-3.6 (9H), 3.6-4.0 (3H), 4.1-4.5 (3H), 4.88 (1H), 4.9-5.4 (1H), 7.0-7.7 (15H), 7.8-8.0 (1H), 8.35 (1H) and 8.50 (1H).

Example 23

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-Hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-N-[[[(1,1-dimethylethoxy) carbonyl]amino]ethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Intermediate 35 (200mg) in dichloromethane (5ml) was stirred at room temperature with (2-aminoethyl)carbamic acid, 1,1-dimethylethyl ester[8] (61mg) for 3 days. The solvent was evaporated to a foam which was purified by preparative thin-layer chomatography using dichloromethane/methanol (9:1) as developer to give the title compound (113mg) as a white glassy solid, $[\alpha]_D^{20}$ +1.4° (c 0.54,

DMSO), ^{1}H n.m.r. (DMSO-d_6) δ 1.0-1.6 (8H), 1.13 and 1.15 (3H), 1.30 (9H), 1.38 (9H), 1.46-1.48 (3H), 1.6-1.9 (4H), 2.0 (2H), 2.2-2.6 (2H) 2.6-3.2 (8H), 3.4-3.75 (4H), 3.82 (1H), 4.32 (1H), 4.6-5.0 (2H), 6.6-7.4 (6H), 7.85 (1H), 7.9-8.0 (1H), and 8.2 (1H).

8. D.Gigot and M.Penninckx, J.Pharm.Sci., 1984, 73(2), 275.

Example 24

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-N-Aminoethyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]-decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Example 23 (204mg) in dichloromethane (8ml) was stirred at room temperature with trifluoroacetic acid (4ml) for 35min. The reaction solution was poured into a mixture of ethyl acetate (50ml) and saturated aqueous sodium hydrogen carbonate and then the organic phase was separated, dried and evaporated to give the title compound (158mg) as a white foam, $[\alpha]_D^{19}$ -19.8° (c 0.52,DMSO),^{1}H n.m.r. (DMSO-d_6) δ 1.22 (9H), 1.0-1.9 (18H), 2.05 (2H), 2.1-2.6 (2H), 2.6-3.0 (6H), 3.1-3.8 (6H), 3.8-4.15 (2H), 4.28 (1H), 4.5-5.0 (2H), 7.1-7.4 (6H) and 7.4-8.5 (3H).

Example 25

[2R-[2α(R*),4β[2'R*S*,4''R*]]]-4-[[[2-Hydroxy-4-[[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

Intermediate 40 (206mg) in dichloromethane (10ml) was stirred for 5 days with benzylamine (46mg). The mixture was diluted with ethyl acetate and then washed with dilute hydrochloric acid, saturated sodium chloride solution, dried and concentrated to a foam. Purification by column chomatography on silica gel (Merck Kieselgel 60, 60g) using dichloromethane/methanol (9:1) as eluant gave the title compound (104mg) as a light yellow foam, $[\alpha]_D^{19}$ + 15.3° (c 0.50, DMSO).

^{1}H n.m.r. (DMSO-d_6) δ 1.17 (3H), 1.28 (9H), 1.50 (3H), 2.2-2.6 (2H), 2.6-3.1 (2H), 3.1-3.6 (6H), 3.68 (1H), 3.8-4.0 (2H), 4.05 (1H), 4.16-4.38 (2H), 4.44 (1H), 4.88 (1H), 5.0-5.2 (1H), 7.1-7.3 (10H), 7.3-7.5 (1H), 7.7-7.9 (1H), 8.35 (1H) and 8.5 (1H).

Example 26

2R-[2α(R*),4β[2'R*S*,1'S*]]]-4-[[[3-[[1-Cyclohexylmethyl-2-oxo-2-[(1,1-dimethylethyl)amino]ethyl]amino]-2-hydroxypropyl]amino]carbonyl]-N-ethylamino-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

6M-Hydrogen chloride in 1,4-dioxan (1ml) was added to a solution of Intermediate 43 (0.155g) in 1,4-dioxan (2ml) at room temperature. The solution was stirred at room temperature for 2h and the solvent removed in vacuo to afford a gummy solid (0.127g). The solid was dissolved in dimethylformamide (5ml) and diisopropylethylamine (220μl), Intermediate 8 and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.124g) added. After stirring at room temperature for 2h the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and evaporated in vacuo to afford a yellow oil. Purification by silica gel column chomatography using chloroform/methanol 50:1 as eluant gave the title compound (63mg), m.p. 99-102°, $[\alpha]_D^{23}$ +30.0° (c 0.5, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 0.7-0.9 (3H), 0.98 (3H), 1.16 (3H), 1.25 (9H), 1.0-1.4 (6H), 1.48 (3H), 1.50-1.80 (6H), 2.30-2.60 (2H), 2.8-3.15 (3H), 3.15-3.80 (5H), 3.78 (1H), 4.30 (1H), 4.75-4.95 (1H), 4.83 (1H), 7.10-7.40 (5H), 7.40-7.80 (1H), 7.80 (1H), 7.89 (1H) and 8.20 (1H).

Example 27

[2R-[2α(R*),4β[2'R*S*,1''S*]]]-4-[[[3-[[1-Cyclohexylmethyl-2-oxo-2-[(1,1-dimethylethyl)amino]ethyl]methylamino]-2-hydroxypropyl]amino]carbonyl]-N-ethylamino-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

8.2M Hydrogen chloride in 1,4-dioxan (2ml) was added to a solution of Intermediate 48 (0.275g) in 1,4-dioxan (6ml) at room temperature. The solution

was stirred at room temperature for 1.5h and the solvent then removed in vacuo to afford a yellow oil (0.179g). The oil was dissolved in dimethylformamide (5ml) and diisopropylethylamine (0.248ml), Intermediate 8 (0.174g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.162g) added. After stirring at room temperature for 1½h the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and the solvent evaporated in vacuo to a pink oil. Purification by silica gel column chomatography using chloroform/methanol 40:1 as eluant afforded the title compound (28mg), m.p. 77-81°, $[\alpha]_D^{23}$ +52.8° (c 0.81, methanol), ^1H n.m.r. (DMSO-d_6) δ 1.13 (3H), 1.24 (9H), 1.46 (3H), 0.8-1.7 (16H), 2.1-2.6 (4H), 2.78 (1H), 2.95-3.2 (4H), 3.2-3.7 (5H), 3.80 (1H), 4.30 (1H), 4.64 and 4.84 (1H), 4.84 (1H), 7.1-7.35 (5H), 7.40 and 7.54 (1H), 7.78 (1H), 7.93 (1H) and 8.21 (1H).

Example 28

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-N-Heptyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

n-Heptylamine (0.165ml) was added to a solution of Intermediate 35 (0.35g) in dichloromethane (5ml) and the mixture stirred at room temperature for 17h. The solvent was then evaporated in vacuo and the residue purified by silica gel column chomatography using chloroform/methanol (50:1) as eluant to afford the title compound (65mg), m.p. 98-103°, $[\alpha]_D^{23}$ -5.6° (c 0.98, methanol), ^1H n.m.r. δ 1.15 to 1.18 (3H), 1.22 and 1.28 (9H), 1.50 and 1.52 (3H), 0.8 to 2.6 (29H), 2.7 to 3.2 (4H), 3.3 to 4.1 (6H), 4.38 (1H), 4.7 to 5.0 (2H), 7.1 to 7.5 (6H), 7.7 to 8.0 (2H) and 8.3 (1H).

Example 29

[2R-[2α(R*),4β[2'R*S*,2''S*,4''R*]]]-4-[[[2-Hydroxy-3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(1,1-dimethylethoxy)-1-

pyrrolidinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

8.4M Hydrogen chloride in 1,4-dioxan (0.94ml) was added to a solution of Intermediate 51 (0.452g) in methanol (7.2ml) at room temperature. The solution was stirred 17h and the solvent removed in vacuo to afford a white solid (0.475g). A portion of the solid (0.36g) was dissolved in dimethylformamide (15ml) and [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.41g), diisopropylethylamine (0.49ml) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.3g) added sequentially. The reaction was stirred at room temperature for 2h and then partitioned between ethyl acetate and water. The organic phase was separated, washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and the solvent evaporated in vacuo to afford a yellow solid. Purification by silica gel column chomatography using chloroform/methanol 50:1 as eluant gave the title compound (0.12g), m.p. 95-100°, $[\alpha]_D^{22}$ +16.2° (c 1.05, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.07 (9H), 1.15 (3H), 1.24 (9H), 1.80 (2H), 2.15 (1H), 2.3-2.5 (2H), 2.98 (2H), 3.1-3.4 (2H), 3.4-3.7 (4H), 3.88 (1H), 4.0-4.5 (3H), 4.45 (1H), 4.88 (1H), 4.78-5.05 (1H), 7.1-7.35 (10H), 7.38 and 7.55 (1H), 7.85 (1H), 8,33 (1H) and 8.48 (1H).

Example 30

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-N-Cyclohexylmethyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Cyclohexylmethylamine (0.146ml) was added to a solution of Intermediate 35 (0.35g) in dichloromethane (5ml) and the mixture stirred for 17h at room temperature. The solvent was evaporated in vacuo and the residue purified by silica gel column chomatography using chloroform/methanol (50:1) as eluant to afford the title compound (43mg) m.p. 115-118°, $[\alpha]_D^{23}$ -3.8° (c 0.53, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 0.82 (3H), 1.0-1.9 (19H), 1.26 (9H), 1.18 (3H), 1.50 (3H),

2.05 (2H), 2.28 (1H), 2.5 (1H), 2.7-3.3 (6H), 3.40-3.55 (3H), 3.60 (1H), 3.80 (1H), 4.33 (1H), 4.82 (1H), 4.90 (1H), 7.1-7.4 (6H), 7.85 (2H) and 8.24 (1H).
(1H), 8.39 (1H), 8.50 (1H).

Example 31

[2R-[2α(R*),4β[2'R*S*,2''R*,4''S*]]]-5,5-Dimethyl-4-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2-hydroxypropyl]amino]carbonyl]-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

6M Hydrogen chloride in 1,4-dioxan (2ml) was added to a solution of Intermediate 53 (0.48g) in 1,4-dioxan (4ml) and the mixture stirred at room temperature for 2h. The solvent was then evaporated in vacuo to afford a white solid (0.45g). The solid was dissolved in dimethylformamide (10ml) and diisopropylethylamine (0.676ml), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (0.559g) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.38g) were added sequentially. The mixture was stirred at room temperature for 2h and then partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent evaporated in vacuo to leave a yellow oil. Purification by silica gel column chomatography using chloroform/methanol (50:1) as eluant afforded the title compound (0.1g) as a white solid, m.p. 74-78°, $[\alpha]_D^{23}$ +24.0° (c 1.0, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.10 (3H), 1.18 and 2.12 (9H), 1.50 (3H), 1.85 (1H), 2.1 - 2.6 (4H), 2.7 - 3.2 (2H), 3.2 - 3.4 (1H), 3.4 - 3.7 (4H), 3.86 (1H), 4.08 (1H), 4.15 - 4.5 (5H), 4.82 (0.5H), 4.90 (1H), 5.08 (0.5H), 7.1 - 7.4 (15H), 7.40 (0.5H), 7.68 (0.5H), 7.83 (1H), 8.33 (1H) and 8.50 (1H).

Example 32

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-Hydroxy-3-[[[(1,1-(dimethylethyl)amino]carbonyl]decahydro-2-

isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Intermediate 54 (250mg) was stirred for 48h at room temperature in a mixture of tetrahydrofuran (10ml) and concentrated ammonia solution (0.3ml). The solution was then concentrated to an orange foam which was purified by column chomatography on silica gel (Merck 9385, 70g) using chloroform:methanol (17:1) as eluant to yield the title compound (133mg) as a white solid, m.p. 132-142° (slow melt), $[\alpha]_D^{21}$ -12.7° (c 1.02, methanol), ^{1}H n.m.r. (DMSO-d_6), 1.15 (3H), 1.24 (9H), 1.50 (3H), 2.2-1.1 (14H), 2.30 (1H), 2.55 (1H), 2.7-3.0 (2H), 3.48 (2H), 3.5-3.8 (3H), 3.96 (1H), 4.30 (1H), 4.70 (1H), 4.93 (1H), 7.0-7.4 (8H), 7.91 (1H) and 8.25 (1H).

Example 33

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-Ethyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Intermediate 54 (250mg) was stirred in dichloromethane (10ml) at room temperature with ethylamine in dichloromethane (10% by volume 0.52ml) for 48h. The mixture was concentrated in vacuo to an orange oil which was purified by column chomatography (Merck 9385, 60g) using chloroform:methanol (50:1) to yield the title compound (75mg) as a white solid, m.p. 96-120° (slow melt), $[\alpha]_D^{21}$ -6.1° (c 0.98, methanol) ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.25 (9H), 1.5 (3H), 1.1 - 2.2 (14H), 2.30 (1H), 2.55 (1H), 2.78 (1H), 2.9 (1H), 3.40 (3H), 3.49 (2H), 3.8 - 3.5 (3H), 3.98 (1H), 4.30 (1H), 4.70 (1H), 4.95 (1H), 7.1 - 7.4 (6H), 8.05 (1H) and 8.49 (1H).

Example 34

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-[4-[(Dimethylamino)phenyl]methyl]-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

A mixture containing Intermediate 54 (250mg), diisopropylethylamine (0.33ml) and p-dimethylaminobenzylamine dihydrochloride (107mg) was stirred at room temperature for 120h. The mixture was washed with water (10ml) and saturated sodium hydrogen carbonate (10ml), dried and concentrated to an orange oil which was purified by column chomatography (Merck 9385, 60g) using chloroform:methanol (50:1) to yield the title compound (99mg) as a white solid, m.p. 108-116° (slow melt), $[\alpha]_D^{21}$ -0.98° (c 1.03, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.24 (9H), 1.50 (3H) 1-1 - 2.2 (14H), 2.30 (1H), 2.55 (1H), 2.7 - 3.0 (2H), 2.88 (6H), 3.49 (2H), 3.5 - 3.8 (3H), 3.90 (1H), 4.0 - 4.30 (2H), 4.38 (1H), 4.70 (1H), 4.92 (1H), 6.62 (2H), 7.03 (2H), 7.1 - 7.4 (6H), 7.91 (1H), 8.20 (1H) and 8.35 (1H).

Example 35

[2R-[2α(R*),4β[2'S*,1''S,4a''S,8a''R]]]-5,5-Dimethyl-4-[[[2-hydroxy-3-[1-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid methyl ester

Intermediate 54 (250mg) was loaded onto a silica column (Merck 9385, 60g) and eluted with chloroform:methanol (50:1) to give the title compound (102mg) as a white solid. m.p. 98-106° (softens), $[\alpha]_D^{21}$ -13.3° (c 0.98, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.25 (9H), 1.5 (3H), 1.1 - 2.2 (14H), 2.30 (1H), 2.55 (1H), 2.78 (1H), 2.90 (1H), 3.40 (3H), 3.49 (2H), 3.5 - 3.8 (3H), 3.98 (1H), 4.30 (1H), 4.70 (1H), 4.95 (1H), 7.1 - 7.4 (6H), 8.05 (1H) and 8.49 (1H).

Example 36

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-α-[[4-(Fluorophenyl)acetyl] amino]-4-[[[3-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]-2-hydroxypropyl]amino]carbonyl]-N-(2-pyridinylmethyl)-2-thiazolidineacetamide

Intermediate 15, isomer 2 (130mg) in 1,4-dioxan (5ml) was stirred for 20h with ~8M hydrogen chloride in 1,4-dioxan (3.0ml) under N_2 at room temperature. The mixture was concentrated to a white solid and re-dissolved in dimethylformamide (10ml) to which was added N-ethyldiisopropylamine (0.19ml),

2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (127mg) and Intermediate 6 (170mg), and the mixture was stirred at room temperature for 20h. Water (20ml) was then added and the solution extracted with ethyl acetate (20ml). The aqueous layer was further washed with ethyl acetate (2x10ml). Combined organic layers washed with saturated sodium bicarbonate (30ml) and saturated sodium chloride (30ml), dried and evaporated to an orange foam (0.30g), re-dissolved in dichloromethane (10ml) and stirred at room temperature for 48h with 2-aminomethylpyridine (45μl). The mixture was concentrated to a pale orange foam and purified by column chomatography on silica gel (Merck 9385, 65g) using chloroform:methanol (30:1) to yield the title compound (48mg), m.p. 120-128° (slow melt), $[\alpha]_D^{21}$ -8.1° (c 0.98, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.25 (9H), 1.50 (3H), 1.1 - 2.2 (14H), 2.30 (1H), 2.58 (1H), 2.78 (1H), 2.90 (1H), 3.50 (2H), 3.55 - 3.8 (3H), 3.96 (1H), 4.34 (2H), 4.44 (1H), 4.70 (1H), 5.0 (1H), 7.0 - 7.15 (2H), 7.15 - 7.4 (5H), 7.70 (1H), 7.99 (1H) and 8.3 - 8.6 (3H).

Example 37

[2R-[2α(R*),4β[2'R*S*,2''S*]]]-5,5-Dimethyl-4-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2-hydroxypropyl]amino]carbonyl]-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

Intermediate 56 (150mg) in 1,4-dioxan (5ml) was stirred for 7h with 3M hydrogen chloride in 1,4-dioxan (2ml) at room temperature. The mixture was concentrated to a white solid and re-dissolved in dimethylformamide (5ml) to which was added N-ethyldiisopropylamine (0.23ml), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (154mg) and [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (193mg). The mixture was stirred at room temperature under N_2 for 16h. Water (10ml) was then added and the solution extracted with ethyl acetate (3x10ml). The combined organic fractions were then washed with saturated sodium hydrogen carbonate (20ml) and saturated sodium chloride (20ml), dried and concentrated to a yellow oil. This oil was purified by column chomatography on silica gel (Merck 9385, 25g) using chloroform:methanol (50:1)

to give the title compound as a white solid (92mg) as a 3:2 mixture of diastereoisomers, m.p. 78-90° (slow melt) $[\alpha]_D^{21}$ +18.2° (c 0.98, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.25 (9H), 1.50 (3H), 1.1 - 1.8 (3H), 2.0 (1H), 2.1 -2.6 (3H), 2.7 - 3.0 (2H), 3.0 - 3.4 (2H), 3.4 - 3.7 (2H), 3.49 (2H), 3.90 (1H), 4.1 - 4.4 (2H), 4.40 (1H), 4.85 (1.5H), 5.12 (0.5H), 7.1 - 7.4 (10H), 7.46 (0.5H), 7.68 (0.5H), 7.92 (1H), 8.38 (1H) and 8.52 (1H).

Example 38

[2R-[2α(R*),4β[2'R*S*,4''S*]]]-4-[[[3-[4-[[(1,1-dimethylethyl)amino]carbonyl]-5,5-dimethyl-3-thiazolidinyl]-2-hydroxypropyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide

Intermediate 58 (as a 1:1 mixture of isomer 1 and isomer 2) (160mg) in 1,4-dioxan (5ml) was stirred with 3M hydrogen chloride in 1,4-dioxan (2ml) at room temperature for 20h. The mixture was concentrated to a white solid and re-dissolved in dimethylformamide (6ml) to which was added N-diisopropylethylamine (0.22ml), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (145mg) and [2R-2α(R*),4β]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (180mg). The mixture was stirred at room temperature under N_2 for 16h. Water (20ml) was then added and the solution extracted with ethyl acetate (3x10ml). The combined organic fractions were then washed with saturated sodium bicarbonate (20ml) and saturated sodium chloride (20ml), dried and concentrated to an oil (0.32g). This oil was purified by column chomatography on silica gel (Merck 9385, 60g) using chloroform:methanol (50:1) as eluant to give the title compound as a white solid (142mg) (1:1 mixture of diasterioisomers). m.p. 95-111° (slow melt), $[\alpha]_D^{21}$ -32.8° (c 0.94, methanol), ^{1}H n.m.r. (DMSO-d_6). δ 1.15 (3H), 1.25 (9H), 1.30 (3H), 1.50 (6H), 2.58 (2H), 2.95 (1H), 3.4-3.1 (2H), 3.7-3.4 (2H), 3.50 (2H), 4.0-3.7 (2H), 4.5-4.1 (4H), 5.90 (1.5H), 5.28 (0.5H), 7.1 - 7.4 (10H), 7.43 (0.5H), 7.66 (0.5H), 7.88 (1H), 8.38 (1H) and 8.52 (1H).

Example 39

[2R-[2α(R*),4β[2'R*,4''R*S]]]-4-[[[3-[2,2,5,5-tetramethyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-3-thiazolidinyl]-2-hydroxypropyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-2-thiazolidineacetamide

Intermediate 60 (145mg) in 1,4-dioxan (2ml) was stirred for 2h with 8.5M hydrogen chloride in 1,4-dioxan (1ml). The solution was evaporated in vacuo to leave a white solid which was dissolved in dry dimethylformamide (4ml) and diisopropylethylamine (221μl), [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (171mg) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (113mg) added. After stirring at room temperature for 17h the reaction mixture was partitioned between ethyl acetate and water and the combined organic extracts washed with saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), and evaporated in vacuo to a yellow oil. Purification by silica gel column chomatography (Merck 9385) using chloroform/methanol (50:1) as eluant gave the title compound (111mg) as a white solid, m.p. 140-142°, ^1H n.m.r. (DMSO-d_6) δ 1.0-1.6 (27H), 2.1-3.0 (3.5H), 3.1-3.7 (5.5H), 4.1-4.4 (2H), 4.43 (1H), 4.58 (0.5H), 4.9 (1H), 5.30 (0.5H), 7.1-7.3 (10H), 7.46 (0.5H), 7.75 (0.5H), 7.85 (1H), 8.34 (1H) and 8.50 (1H).

Example 40

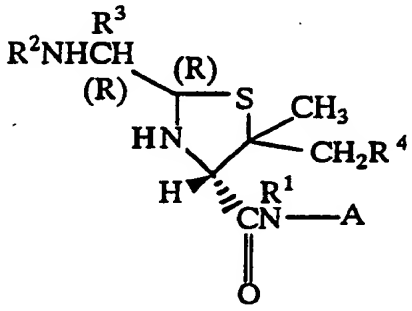
[3RS,2'S,2''R,4''S,1'''R]-4-[3-[[[5,5-dimethyl-2-[[1-[(phenylacetyl)amino]-2-oxo-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]-2-hydroxypropyl]-3-[[(1,1-dimethylethyl)amino]carbonyl]-1-piperazinecarboxylic acid, phenylmethyl ester

2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (65mg) was added to a solution containing Intermediate 65 (103mg), [2R-[2α(R*),4β]]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid (89mg) and diisopropylethylamine (90μl) in dimethylformamide (8ml) and the mixture stirred at room temperature for 20h. The mixture was then diluted with ethyl acetate (200ml) and the solution washed with brine, dried ($MgSO_4$) and the solvent

evaporated in vacuo to give a pale yellow gum. Purification by chomatography on silica plates using ethyl acetate as eluant afforded the title compound as separate diastereomers. Isomer 1 (52mg) as a white solid, m.p. 108-112°, $[\alpha]_D^{21}$ +61.5° (c0.29, methanol), γ_{max} ($CHBr_3$) 3407 (NH), 1674cm^{-1} (C=O), ^1H n.m.r. (DMSO-d_6) δ 1.19 (3H), 1.21 (9H), 1.50 (3H), 2.0 - 2.5 (3H), 2.70 (1H), 2.8 - 3.3 (5H), 3.51 (2H), 3.6 - 4.0 (4H), 4.1 -4.5 (3H), 4.90 (1H), 5.0 - 5.2 (3H), 7.1 - 7.4 (15H), 7.51 (1H), 7.90 (1H), 8.38 (1H), 8.54 (1H). Isomer 2 (41mg) as a colourless foam, $[\alpha]_D^{21}$ +38.1° (c 0.29, methanol), γ_{max} ($CHBr_3$) 1675cm^{-1} (C=O), ^1H n.m.r. (DMSO-d_6) δ 1.19 (3H), 1.21 (9H), 1.51 (3H), 2.1 - 2.5 (3H), 2.82 (1H), 2.9 - 3.4 (3H), 3.50 (2H), 2.69 (2H), 4.96 (1H), 4.27 (2H), 4.43 (1H), 4.88 (2H), 5.08 (2H), 7.1 - 7.4 (15H), 7.61 (1H), 7.90 (1H), 8.40 (1H) and 8.50 (1H).

CLAIMS:

1. Compound of the general formula (I)



(I)

wherein :

R^1 is hydrogen, C_{1-4}alkyl or CH_2C_{1-3}alkyl where the C_{1-3}alkyl portion is substituted by OH;

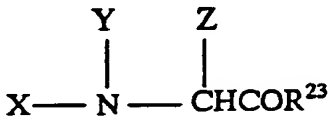
R^2 is hydrogen, C_{1-10}alkyl, C_{3-8}cycloalkyl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, COAr, COHet, $COCH_2R^5$, COCH(OH)Ar, COCH(OH)Het, COCH=CHPh, COR^6, CO_2CH_2Ar, CO_2CH_2Het, SO_2Ar, SO_2Het, $SO_2CH_2R^7$ SO_2CH=CHPh or SO_2R^8 [where R^5 and R^7 each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, aryloxy, heteroaryloxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_nCO_2R^9$ (where n is zero or 1 and R^9 is hydrogen or C_{1-6}alkyl), $(CH_2)_mNR^{10}R^{11}$ (where m is zero, 1, 2, 3, 4 or 5 and R^{10} and R^{11} are each independently hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), and R^6 and R^8 each independently represent C_{3-8}cycloalkyl substituted by phenyl];

R^3 is hydrogen, C_{1-6}alkyl, $COOR^{12}$ (where R^{12} is hydrogen, C_{1-6}alkyl or ArC_{1-4}alkyl) or $CONR^{13}R^{14}$ [where R^{13} is hydrogen or C_{1-4}alkyl and R^{14} is hydrogen, OH, aryl, heteroaryl, ArC_{1-4}alkyl, (wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl), $HetC_{1-4}$alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_pR^{15}$ (where p is zero or 1 and R^{15} is CF_3 or CO_2R^{16} where R^{16} is hydrogen or C_{1-6}alkyl), $(CH_2)qNR^{17}R^{18}$ (where q is zero, 1, 2, 3, 4 or 5 and R^{17} and R^{18} are each independently hydrogen, C_{1-4}alkyl or aryl or together with the nitrogen atom to which they are attached form a saturated

heterocyclic amino group), $CHArCO_2R^{19}$, $CHHetCO_2R^{20}$ (where R^{19} and R^{20} are each independently hydrogen or C_{1-6}alkyl) or C_{1-6}alkyl optionally substituted by OH, or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group];

R^4 is hydrogen, hydroxy, or acetoxy;

A represents either a group $CH^{21}CH^{22}OH$ or a group



[where R^{21} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl or ArC_{1-4}alkyl, R^{22} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl, ArC_{1-4}alkyl, $CH^{24}CONR^{25}R^{26}$ (where R^{24} is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl or ArC_{1-4}alkyl, R^{25} is hydrogen or methyl and R^{26} is hydrogen, C_{1-6}alkyl optionally substitued by one or two hydroxyl groups, aryl, heteroaryl, C_{3-8}cycloalkylC_{1-4}alkyl, ArC_{1-4}alkyl wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl, or $HetC_{1-4}$alkyl) or $CH^{24}NHCOR^{27}$ (where R^{27} is C_{1-6} alkyl, C_{3-8} cycloalkylC_{1-4}-alkyl or ArC_{1-4} alkyl), R^{23} is C_{1-6}alkoxy or $NR^{28}R^{29}$ (where R^{28} is hydrogen or methyl and R^{29} is hydrogen, C_{1-4}alkyl, aryl, ArC_{1-4}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl);

X is a group

$$-CHR^{30}(CHR^{31})_r(CHR^{32})_sCHR^{33}-$$

where R^{30} and R^{33} are hydrogen, r is 1, s is zero and R^{31} is hydroxyl or hydroxymethyl, or R^{30} and R^{33} are hydrogen, r and s are 1 and R^{31} and R^{32} are each hydrogen or hydroxyl provided that at least one of R^{31} and R^{32} is hydroxyl, or one of R^{30} and R^{33} is hydrogen and the other is hydroxymethyl and r and s are zero;

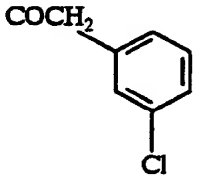
Y is a methyl group and Z is a C_5 or C_6 cycloalkylmethyl group or Y and Z together represent a trimethylene or tetramethylene group in which one of the $-CH_2-$ groups is optionally replaced by -O-, -S- or $-NR^{34}-$ (where R^{34} is hydrogen, C_{1-6}alkyl, ArC_{1-4}alkyl, COR^{35}, CO_2R^{35} or $CONH^{35}$ where R^{35} is C_{1-6}alkyl, aryl, ArC_{1-4}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl) and one or more of the $-CH_2-$ groups is optionally substituted by a C_{1-6}alkyl, C_{1-6}alkoxy, aryl, ArC_{1-4}alkyl, ArC_{1-4}alkoxy or heteroaryl group or by two C_{1-6}alkyl groups, or Y and Z together represent a trimethylene or tetramethylene group fused to a benzene ring or to a 5 or 6 membered cycloalkane or cycloalkene ring];

and physiologically acceptable salts and solvates thereof.

2. Compounds according to Claim 1 wherein R^1 represents a hydrogen atom or a methyl group.

3. Compounds according to Claim 1 or Claim 2 wherein R^2 represents a group selected from COAr (where Ar is biphenyl), $COCH_2R^5$ (where R^5 is C_{1-6} alkyl, aryl, heteroaryl, aryloxy or ArC_{1-4}alkyl) or COR^6 (where R^6 is cyclopropyl substituted by phenyl).

4. Compounds according to Claim 1 or Claim 2 wherein R^2 represents $COCH_2Ph$,



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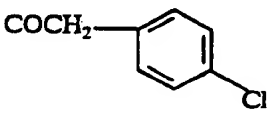

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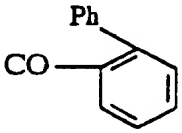

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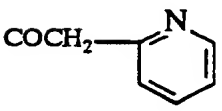


,

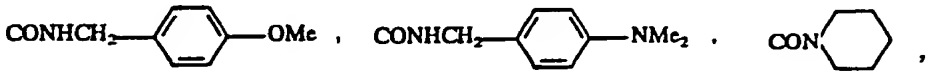

,

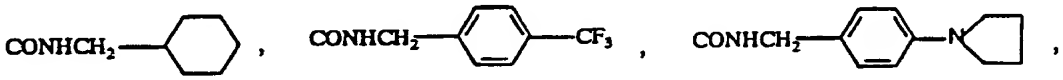
$COCH_2OPh$, $CO(CH_2)_2Ph$ or $COCH_2Pr\text{-}i$.

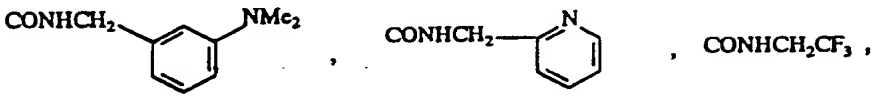
5. Compounds according to any preceding claim wherein R^3 represents a group $CONR^{13}R^{14}$.

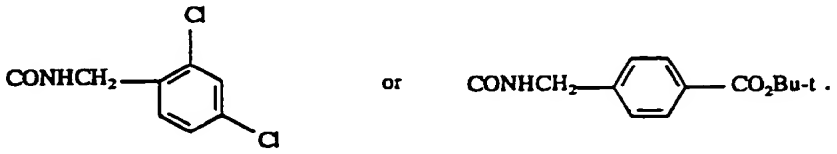
6. Compounds according to Claim 5 wherein R^{13} is hydrogen and R^{14} is a group selected from ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, C_{3-8} cycloalkylmethyl or CH_2CF_3 or R^{13} is hydrogen or methyl and R^{14} is methyl or ethyl or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a piperidino group.

7. Compounds according to any one of Claims 1 to 4 wherein R^3 represents $CONHCH_2Ph$, $CONHCH_2CH_3$, $CONHCH_2CH_2Ph$, $COMe_2$,





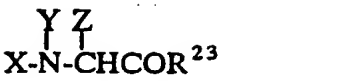




8. Compounds according to any preceding claim wherein R^1 is hydrogen and A represents a group $CH^{21}CH(OH)CH_2CONH^{26}$.

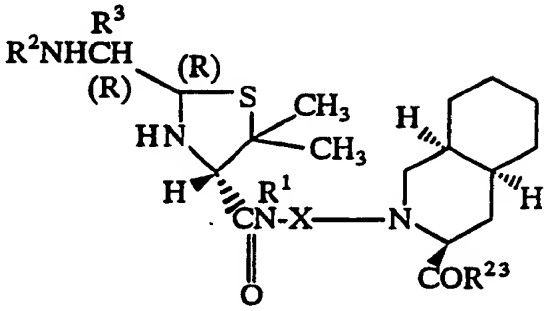
9. Compounds according to Claim 8 wherein R^{21} represents ArC_{1-4} alkyl and R^{26} represents ArC_{1-4}alkyl or $HetC_{1-4}$alkyl.

10. Compounds according to any one of Claims 1 to 7 wherein A represents a group



in which the group NY-CHZ forms a monocyclic or bicyclic system as defined in Claim 1 above.

11. Compounds of the formula (Ia)



(Ia)

and physiologically acceptable salts and solvates thereof.

12. A compound according to Claim 1 selected from:

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]-decahydro-2-isoquinolinyl] propyl]amino]carbonyl]-5,5-dimethyl-N-[[[(1,1-dimethylethoxy) carbonyl] amino]ethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'R*S*,3''S*,4a''S*,8a''R*]]]-N-cyclohexylmethyl-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-4-[[[2-hydroxy-3-[[[(1,1-(dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-ethyl-4-[[[2-hydroxy-3-[[[(1,1-(dimethylethyl)amino]carbonyl]decahydro-2-

isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-N-[4-[(dimethylamino)phenyl]methyl]-4-[[[2-hydroxy-3-[[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β[2'S*,1''S,4a''S,8a''R]]]-5,5-dimethyl-4-[[[2-hydroxy-3-[1-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]propyl]amino]carbonyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid methyl ester; and

[2R-[2α(R*),4β[2'S*,3''S*,4a''S*,8a''R*]]]-α-[[4-(fluorophenyl)acetyl] amino]-4-[[[-3-[[(1,1-dimethylethyl)amino]carbonyl]decahydro-2-isoquinolinyl]-2-hydroxypropyl]amino]carbonyl]-N-(2-pyridinylmethyl)-2-thiazolidineacetamide;

13. A compound according to Claim 1 selected from:

2R-[2α(R*),4β(2'S*,3''S*,4a''S*,8a''R*)]-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-(2-phenyl-1-hydroxymethyl)ethyl]amino]carbonyl]-2-thiazolidineacetamide;

2R-[2α(R*),4β(R*,R*)-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[(2-hydroxy)-4-[[(1H-benzimidazol-2-yl)methyl]amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-thiazolidineacetamide:

and 2R-[2α(R*),4β(R*,R*)-5,5-dimethyl-α-[(phenylacetyl)amino]-N-phenylmethyl-4-[[[1-[(2-hydroxy)-4-[(phenylmethyl)amino]-4-oxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-thiazolidineacetamide and physiologically acceptable salts and solvates thereof.

14. A compound according to any one of Claims 1 to 13 or a physiologically acceptable salt or solvate thereof for use as a therapeutically active agent.

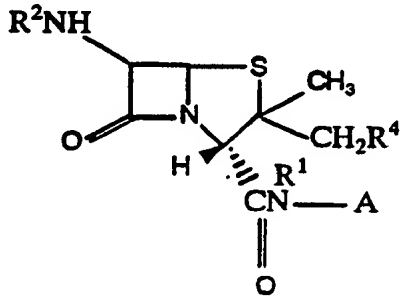
15. A compound according to any one of Claims 1 to 13 or a physiologically acceptable salt or solvate thereof for use in the treatment of a viral infection.

16. Use of a compound according to any one of Claims 1 to 13 or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a retroviral infection.

17. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 13 or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers.

18. A process for preparing a compound according to Claim 1 or a physiologically acceptable salt or solvate thereof, which comprises:

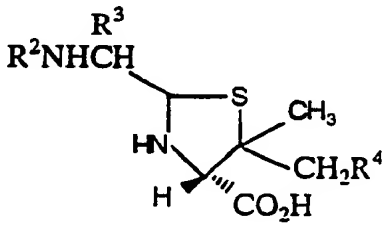
(A) in preparing compounds in which R^3 represents $COOR^{12}$ or $CONR^{13}R^{14}$, treating compounds of formula (II)



(II)

or protected derivatives thereof with a nucleophile $R^{12}OH$ or $R^{13}R^{14}NH$, followed, where necessary, by the removal of any protecting groups present;

(B) coupling the carboxylic acids of formula (III)



(III)

or salts and/or protected derivatives thereof with a diamine of formula (IV)

$$H^1NA \qquad (IV)$$

or a protected derivative thereof, followed, where necessary, by the removal of any protecting groups present; or

(C) interconverting compounds of formula (I);

and if necessary or desired subjecting the compounds resulting from any of steps (A) to (C) above to a further reaction comprising : converting a compound of formula (I) or a salt thereof into a physiologically acceptable salt thereof.

19. Compounds of formula (II).

20. A method for the treatment of a viral infection in a mammal comprising administering to said mammal a therapeutically effective amount of a compound as claimed in Claim 1 or a physiologically acceptable salt or solvate thereof.

21. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 13 or a physiologically acceptable salt or solvate thereof for use in the treatment of a viral infection in a mammal.

22. Compounds according to any one of Claims 1 to 13 substantially as herein described.

23. Compositions according to Claim 17 or Claim 21 substantially as herein described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01494

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 217/06 A 61 K 31/425 C 07 D 417/12
C 07 D 499/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0346847 (F. HOFFMANN-LA ROCHE) 20 December 1989, see claims; pages 13,14,36,37 ---	1,20,21
A	Journal of Medicinal Chemistry, vol. 33, no. 10, October 1990, (Washington, DC, US), R.B. GAMMILL et al.: "Structure-based, C2 symmetrie inhibitors of HIV protease", pages 2687-2689 ---	
A	Journal of Medicinal Chemistry, vol. 33, no. 5, May 1990, (Washington, DC, US), D.H. RICH et al.: "Hydroxyethylamine analogues of the p17/p24 substrate cleavage site are tight-binding inhibitors of HIV protease", pages 1285-1288 -----	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08-09-1992	21. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/ 01494

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 20 is directed to a method of treatment of the human body by therapy the search has been carried out and based on the alleged effects of the compounds.
Claims not searched 22-23: See Rule 29 (6) PCT

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9201494
SA 61915

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0346847	20-12-89	AU-B- 624144	04-06-92
		AU-A- 3613089	14-12-89
		JP-A- 2042048	13-02-90